FEB 19 1917

VOLUME 19 NUMBER 2

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FEBRUARY 15, 1917

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879

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OSTEOGENESIS IMPERFECTA *

JULIUS H. HESS, M.D.
CHICAGO

DEFINITION

Osteogenesis imperfecta is a rare systemic disease of unknown etiology, characterized by imperfect development of bones. Increased absorption of deficiently formed bony trabeculae leads to deficient formation of cortex and spongiosa, which results in osteoporosis. Clinically it is characterized by multiple intraperiosteal fractures, usually with little displacement of fragments and excessive callus formation. It occurs in two clinical forms, namely, osteogenesis imperfecta congenita and osteogenesis imperfecta tarda.

SYNONYMS

The name osteogenesis imperfecta congenita was coined by Vrolik[1] in 1845. Although a number of other names have been proposed for this disease, Vrolik's designation seems to be the best, since it is derived from pathology of the disease and does not assume or presuppose anything. Synonyms for this disease are as follows: osteomalacia congenita, because in some cases the bones are abnormally pliable; rachitis fœtalis annularis, because of the excessive callus formation at the seat of fractures; malacia myeloplastica (von Recklinghausen[2]), periosteal dysplasia (Durante[3]), dystrophie periostale (France), ostitis parenchymatosa chronica (Schmidt[4]), micromelia annularis, osteoporosis congenita (Kundrat), fragilitas ossium (Klebs), from the chief symptom, which is fragility of the bones. Fragility of the bones, however, is present also in other diseases, among others rachitis, osteomalacia, scurvy, tuberculosis, hereditary syphilis and miscellaneous neoplasms. In these cases, however, it is secondary, while in

* Submitted for publication July 18, 1916.

1. Vrolik: Tabul. ad illustrandam embryogenesin. hominis et mammalium, Amstelodami, 1845, Tab. 91.

2. Von Recklinghausen: Untersuchungen über Rachitis und Osteomalazie, Fischer, Jena, 1910.

3. Durante: La dysplasie périostale, Acad. de méd., 1905.

4. Schmidt: Ein Beitrag zur Kenntnis der sogennanten Osteopsathyrosis congenita, Inaug.-Dis., Leipzig, 1901; Abnorme Knochenbrüchigkeit bei einem Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk., **14.**

osteogenesis imperfecta congenita the fragility of the bones is a primary manifestation.

Osteopsathyrosis idiopathica is a name which was given by Lobstein[5] in 1833 to a disease which in its pathology and symptoms resembles the osteogenesis imperfecta; however, he described it as occurring in older infants and children. Today these two diseases are regarded as identical processes, Lobstein's description corresponding to osteogenesis imperfecta tarda. Looser[6] also thinks that "the so-called idiopathic osteopsathyrosis and the osteogenesis imperfecta are pathologically identical diseases. As to the clinical onset of the disease, all imaginable transitions are present between the congenital affection and one appearing only in later infancy or childhood. Even those cases of osteogenesis imperfecta (in broader sense) that make their appearance in childhood are probably to be traced back to congenital changes. Durante[8] says that osteopsathyrosis of the adult represents an atypical form of osteogenesis imperfecta. Miura[7] speaks of a secondary osteopsathyrosis which occurs in childhood and is due to rickets, osteomalacia, Barlow's disease, tuberculosis, hereditary syphilis and miscellaneous neoplasms, in contradistinction to a primary fragility of bones, so-called osteopsathyrosis idiopathica, the pathogenesis of which is not well understood yet. It occurs in two types: The one is congenital and is identified with osteogenesis imperfecta by most authors; the other occurs in early childhood. Summing up the views of different authors as to the relation between osteogenesis imperfecta congenita and osteopsathyrosis idiopathica, Frangenheim[8] says:

> With Looser we are of the opinion that the osteogenesis imperfecta and the idiopathic osteopsathyrosis represent a form of a disease which, as far as histologic behavior of the bones is concerned, has nothing to do with any known disease accompanied by atrophy or softening of the skeleton, the most important symptom of the disease being the abnormal fragility of the bones, which appears at birth or very soon after birth, but may also appear in early or late childhood after a certain period of latency. If we want to separate the osteogenesis imperfecta from the idiopathic osteopsathyrosis, then the difference can be only a clinical one, depending on the time at which the fragility of the bones begins.

According to this there are two forms of osteogenesis imperfecta, one which is congenital (congenita), the symptoms appearing at birth or very soon after birth, and the other a latent form (tarda), in which the symptoms appear in late infancy or childhood, after a variable

5. Lobstein: Lehrb. d. pathol. Anat., 1834, **2**, 179.

6. Looser: Zur Kenntnis der Osteogenesis imperfecta congenita und tarda, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1905, **15**, 161. Ueber Osteogenesis imperfecta tarda, Verhandl. d. deutsch. path. Gesellsch., 1905, p. 239.

7. Miura, S.: Osteopsathyrosis Idiopathica, Jahrb. f. Kinderh., 1911, **73**, 545.

8. Frangenheim: Die Krankheiten des Knochensystems im Kindesalter, Neue Deutsche Chirurgie, Enke, Stuttgart, 1913, **10**.

period of latency, the latter being sometimes called osteopsathyrosis idiopathica. In this respect the disease resembles congenital syphilis, in which the manifestations may appear at birth or very soon after birth, or they may appear in late infancy or childhood, after a variable period of latency.

ETIOLOGY

The direct cause of the disease is not known. There is some evidence which seems to show that the disease may be inherited. Griffith[9] estimated a hereditary factor in 27 per cent. of all cases of osteogenesis imperfecta congenita and in 15 per cent. of cases of osteogenesis imperfecta tarda, these figures being in all probability far too low. Harmer says that it has been transmitted through three generations and it has affected nine of ten children and a child of one of these. Zurhelle[10] reports a case of a child in whose mother he found a deformity of a leg and the Roentgen rays showed healed fractures and osteoporosis. Schmidt[11] mentions a case of a 68-year-old man who suffered many fractures before the 20th year of life, all of them being due to trivial causes. He had two sons. One had fractures at birth and the other suffered numerous fractures in the first year of his life. Gurlt[12] compares the disease with hemophilia, which shows the same territorial distribution, namely, North Germany, England and North America, and states that it is transmitted to the males through unaffected females. Looser and Griffith, however, say that the disease is seldom transmitted through female offspring. Several generations may be affected and one generation may be skipped. The congenital form occurs more frequently in females (Frangenheim[8]), the late form more often in males. Calcium deficiency was suspected to be the cause of the disease and Stoelzner was able to produce changes identical with osteogenesis imperfecta in animals by feeding them with food poor in calcium. Looser, however, remarks that it is very difficult to administer calcium-free food to man, and besides, children suffering with osteogenesis imperfecta received the same food as their parents and brothers and sisters who did not suffer. Prematurity was suggested as a cause also. Syphilis was also suspected; both parents were syphilitic in Vrolik's case and the mother was syphilitic in Henckel's[13] case, but in neither case did the children show

9. Griffith: Idiopathic Osteopsathyrosis (Fragillitas Ossium) in Infancy and Childhood, Am. Jour. Med. Sc., 1897, **113.**

10. Zurhelle: Osteogenesis imperfecta bei Mutter und Kind, Beitrag zur Frage der Identität dieser Erkrankung mit Osteopsathyrosis idiopathica, Ztschr. f. Geburtsh. u. Gynäk., 1913, **74,** 942.

11. Schmidt: Demonstration von Röntgenbilden eines achtjährigen Knaben mit Osteopsathyrosis, München. med. Wchnschr., 1899, No. 22, p. 748.

12. Gurlt: Ueber Knochenbrüchigkeit un über Frakturen durch Muskelaktion, Deutsch. Klin., 1857; Handbook of Bone Fractures, 1862, **1.**

13. Henckel: Neue medizinische und chirurgische Anmerkungen, Berlin, 1772.

any symptoms of syphilis. Glands of internal secretion, especially thyroid and hypophysis, have been searched for the change which may have caused the disease, but no marked changes have been described in these organs.

PATHOGENESIS

The disease consists of imperfect formation of bones. The development of bones is normal up to formation of primary marrow spaces. The spaces are not lined by bony cells, as they should be, and this starts the abnormal development. All observers agree that there is deficient formation of bone, but there are some differences of opinion as to whether the process of absorption of bone, which is a normal process during the growth, remains within normal limits. Thus Axhausen[14] says that the nature of the disease is a deficient enchondral and periosteal bone formation, due to lowered function of osteoblasts and of the periosteal cells, while the preparatory calcification of cartilage and absorption of bone are normal. Segawa,[15] on the other hand, says that the pathologic process in the bone in osteogenesis imperfecta congenita consists of a disproportion between building up and breaking down, which leads to porosis, deficient apposition or increased osteoclastic resorption playing important rôles, individually or combined. These deviations from the normal result in (1) absence of successive thickening of corticalis toward the middle of the diaphysis; (2) the bone formed from the periosteum remains in the primitive stage of fibrous bone; (3) the reticular structure shows wide meshes, the Haversian canals being replaced by large marrow spaces; (4) the osteoporosis in all probability is secondary to excessive formation of the medullary spaces, which again is due to deficient development of the bony substance and to increased absorption. The more remote cause of this maldevelopment is supposed to be embryonal malformation of periosteum and endosteum at the beginning of the process of ossification (Dieterle) or to the circumstance that the osteoblasts that arise from avascular, fibrous bone marrow because of insufficient nutrition do not develop properly, remaining polygonal and low, and later many of them undergoing metaplasia into osteoclasts (Buday[16]). An objection, however, might be made to the latter theory, since avascular, fibrous marrow is not found in all cases.

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14. Axhausen: Osteogenesis imperfecta oder frühe Osteomalazie als Grundlage der idiopathischen Osteopsathyrosis, Deutsch. Ztschr. f. Chir., 1908, **92**, Nos. 1-3; Zur Frage der Osteomalazie im Kindesalter, Gedenkschrift f. v. Leutbold, 1906, **2**.

15. Segawa: Combination of Congenital and Acquired Diseases of the Skeleton (Osteogenesis Imperfecta Congenita, Morbus Barlowii, Rachitis), Ztschr. f. Kinderh., 1915, **12**, 246.

16. Buday: Beitrag zur Lehre von der Osteogenesis imperfecta, Sitzungsberichte d. k. Akademie zu Wien. Math.-naturwissensch, Klasse, 1895, **104**, Nos. 1-5.

PATHOLOGY

The primary pathologic changes are of the same nature in all bones of the body, varying only in degree. These changes are best observed in the bones of the extremities. The bones are either so soft that they may easily be bent or cut with a knife or they are brittle. They may be plump and short or compressed or cylindrical. The shortening is secondary to fractures and bendings, the primary growth in length being normal. Numerous thickenings due to healed fractures may be seen. The convexity of the deformities in the bones are on the extensor surfaces. Bluish white islands of cartilage are seen throughout the spongiosa. Epiphyses are formed by hard hyaline cartilage, which is surrounded by perichondrium. They are richly vascular and the centers of ossification are large. The epiphyseal line is straight. The proliferation zone of cartilage is narrower and somewhat irregular, the cartilage cells being arranged into columns that are about one fourth of the normal height. This is more marked toward the periphery. The calcified cartilage disappears too early, being prematurely absorbed. The bony trabeculae are short and thin and are placed obliquely and transversely to the long axis of the bone, while normally they are more longitudinal. There is a marked preponderance of medullary substance over spongiosa and the lamellar growth of the bone is less marked. The bone marrow is mostly fibrous, poor in cells and surrounded by bony trabeculae. Lymph marrow preponderates in the middle of the diaphyses (Buday[16]). Michel[17] found the marrow to be vascular only in the periphery of the bone and avascular at the epiphyseal line and where the bone is bent. Harbitz[18] described the bone marrow as very vascular and rich in cells, while Stilling[19] says that it is of normal vascularity. Osteoblasts are everywhere markedly diminished in number, but they are somewhat larger and their nuclei are broad and oval. Osteoclasts are strikingly too numerous.

SYMPTOMS

Multiple fractures occurring on very slight provocation are the most prominent characteristic of the disease. Fractures are mostly complete with preserved periosteum, this being regarded by Segawa[15] as of importance for diagnosis. In recent fractures the fragments are connected by fibrous tissue, in older ones by spongiosa. The callus that forms in place of fractures is usually excessive in size, but it is of

17. Michel: Osteogenesis imperfecta, Virchows Arch. f. path. Anat., 1903, 173.

18. Harbitz: Ueber Osteogenesis imperfecta, Beitr. z. path. Anat. u. z. allg. Path., 1901, p. 30.

19. Stilling: Osteogenesis imperfecta, Virchows Arch. f. path. Anat., 1889, **115**, 3.

inferior quality histologically, being porous. The periosteum of the callus is broadened and rich in cells. Bone marrow is abundant, being gelatinous or finely fibrillar. Periosteal callus preponderates over the myelogenous. The callus is laid down in cartilage first, which is followed by metaplasia of cartilage into bone. When the callus is fully developed it consists of a network of calcified bony trabeculae with osteoblastic covering, with islands of hyaline cartilage below the periosteum and irregular arrangement of bony lamellae. The size of the callus depends mainly on the development of germinal and cartilage tissue, while the bone tissue is just as deficient as in other parts of the skeleton (Segawa[15]).

The so-called calvaria membranacea is also characteristic of the disease. The cranial vault resembles a soft rubber sac with mosaic-like inlays of small pieces of bones around the centers of ossification. The fontanels are widely open and abnormally large. The bones may be so brittle that on pressure they easily crumble to pieces. The membranous sac is formed by connective tissue membrane, which is poor in cells. The diploe is not formed. These findings apply especially to osteogenesis imperfecta congenita.

METABOLISM

Schwarz and Bass,[20] who have studied metabolism in a case of osteogenesis imperfecta congenita, found that nitrogen metabolism is approximately normal, fat retention and resorption is normal. Calcium retention was only slightly below the normal, there being, however, a positive calcium balance. In two cases of osteogenesis imperfecta congenita Bookman[21] found that during the active stage phosphorus retention was materially higher than that of two normal children examined by Cronheim and Müller;[22] magnesium retention was low during the active stage, but this increased with the increase in calcium retention during the healing stage, the increase in magnesium retention, however, being less marked than in calcium. As to calcium metabolism, Bookman came to the following conclusions, based on the study of two cases of osteogenesis imperfecta congenita, age approximately 3 and 4 months: 1. In active cases the calcium retention is somewhat below or very decidedly below the normal. 2. It is probable that variations in the course of the disease cause changes in the calcium balance. 3. The deficient retention of calcium is apparently influenced favorably by cod liver oil and phosphorus, and still more strongly by calcium lactate.

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20. Schwarz and Bass: Osteogenesis Imperfecta: Report of a Case with the Study of Its Metabolism, Am. Jour. Dis. Child., 1913, **5**, 131.
21. Bookman, A.: The Metabolism in Osteogenesis Imperfecta with Special Reference to Calcium, Am. Jour. Dis. Child., 1914, **7**, 436.
22. Cronheim and Müller: Biochem. Ztschr., 1908, **9**, 76.

GENERAL SYMPTOMS

The children suffering with this disease are usually mentally underdeveloped, are small and underweight for their age and their skin is soft and delicate. Segawa observed in his case attacks of long-lasting profuse sweating. These attacks started in the second week of life, sweating being especially marked on the head and in the face and this lasted with remissions and recurrences up to death. The head of these children is usually excessive in size in proportion to the trunk and often covered with luxuriant, long, silky hair. The face is small and well developed, palpebral fissure narrow, but the physiognomy is not characteristic. The neck is short, the thorax is flattened, asymmetric, and the ribs show nodules which are calluses remaining after the healing of fractures. In lateral regions of the thorax deep retractions can be seen during breathing and crying. The skin of the thorax is delicate and edematous, subcutaneous tissue being richly developed. From the axillae deep folds extend over the chest. The abdomen is protuberant. The extremities are shortened, curved, angulated, showing calluses of fractures. The feet and hands are small and delicate. Flaccid paralysis of extremities, lowered electrical excitability and nystagmus have been found (Segawa[15]). A majority of children affected with this disease die soon after birth or are stillborn. In those surviving, the fractures may become less frequent with advancing age and the disease may come to a standstill.

The most characteristic symptom of the disease is multiple fractures, as many as 113 having been found by Chaussier.[23] The fractures may occur in series with periods between, during which the patient may be free from fractures. There is little pain associated with them and crepitus is often absent. Healing is more rapid than in normal bone, but marked deformity usually results. It is interesting to note that while fractures heal rapidly, osteotomies that have been undertaken for correction of deformities healed very slowly (Cortes,[24] Doering[25]).

DIAGNOSIS

Roentgen-ray findings are characteristic and diagnostic for the disease. They may be summed up as follows:

1. Multiple, mostly intraperiosteal fractures, often showing areas of bone resorption at the seat of fracture.

2. Excessive callus formation.

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23. Chaussier: Sur les fractures et les luxations observées chez le fétus, etc., Beitr. z. path. Anat. u. z. allg. Path., **19,** (after Feldmann, Ueber Wachstumsanomalien der Knochen).

24. Cortes: L'osteopsatirosis di Lobstein, Zentralbl. f. Chir., 1910, **38,** No. 43.

25. Doering: Beitrag zur Lehre von der idiopathischen Osteopsathyrosis, Deutsch. Ztschr. f. Chir., **77.**

3. Deficient shadow formation seen in all bones of the body, due to increased permeability to Roentgen rays. Often the bone shadows show but little more density than the surrounding soft parts.

4. The diaphyses of long bones may be slender, and only very rarely show any curvature or bending.

5. The cortex is of irregular thickness, on the whole very thin and parchment-like in appearance and may even appear to be absent in some places. There is little or no tendency toward thickening on the concave side of the shaft.

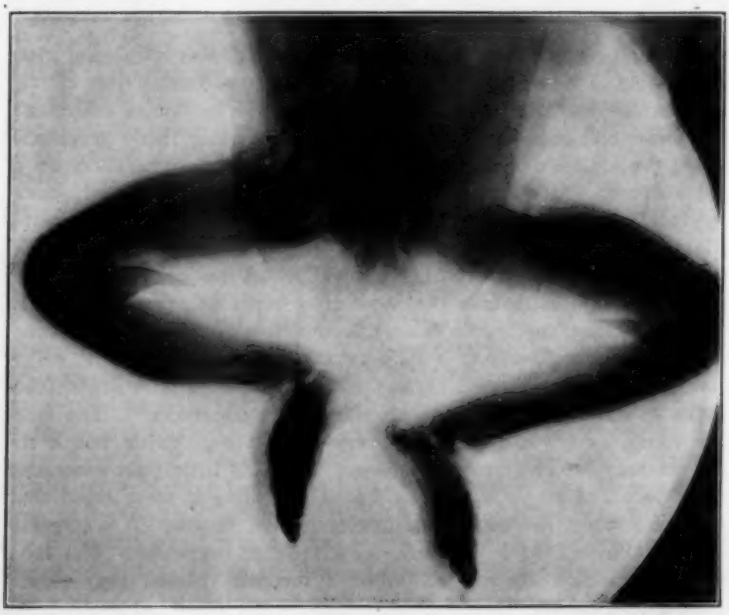

Fig. 1 (Case 1).—Osteogenesis imperfecta, C. R., aged 16 months.

6. The spongiosa contains wide meshes and an absence of structural markings. These changes are not limited to the diaphyses. All bones show this change, but not to the same degree, the most marked changes being found in the bones of the hands.

7. The medullary cavity is increased in size and shows irregularly mottled shadow.

8. The epiphyseal cartilages and their centers of ossification are larger than normal and the epiphyseal lines are straight.

The following cases of osteogenesis imperfecta came under our observation:

CASE 1.—C. R., aged 16 months, was admitted to the service of Dr. I. A. Abt, Michael Reese Hospital, May 10, 1914. Two months before, the mother had noticed that the child was losing markedly, getting weaker and the extremities becoming tender. The child could not stand even when held. She screamed when the limbs were touched and when she was being clothed. The abdomen was distended and the bowels constipated. During the previous month the spine had been turning. There was no history of past illnesses except that of gastro-enteritis. Her personal history revealed that she was one of twins, spontaneous birth. She sat erect at 9 months, but did not learn to talk or walk. She was breast fed until 3 months old; in the second month two bottles a day were substituted for the breast, and at 3 months she was put on the bottle entirely. The family history is negative, but both parents looked weak and emaciated.

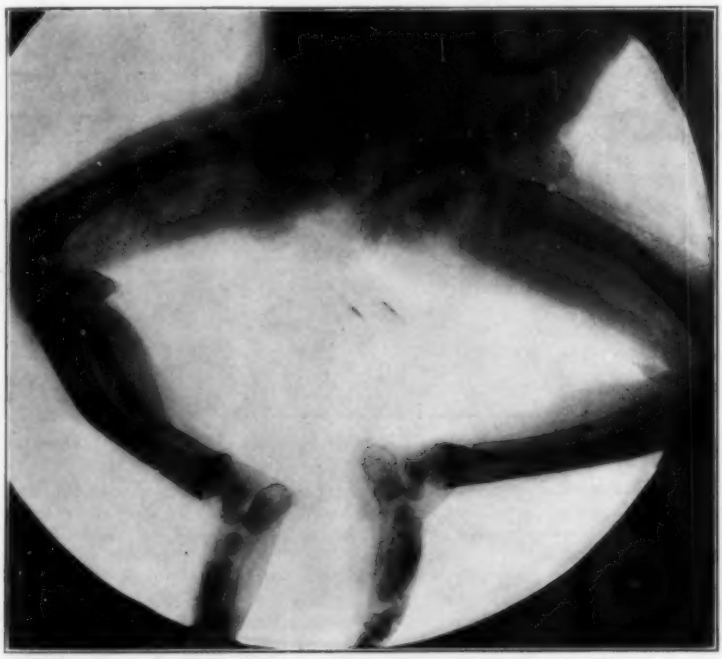

Fig. 2.—Same patient as shown in Figure 1, taken seven weeks later, showing marked improvement.

Examination showed her to be a fairly well nourished child who cried when touched. The lower extremities were drawn up on the abdomen. The head was square shaped and showed marked craniotabes. There was a marked rosary on the ribs and a flaring of lower costal margins; the lung findings were negative. The heart was negative. The abdomen was large and protuberant, somewhat distended. The spleen, liver and kidneys were negative. Lower extremities were flexed, the thighs on the abdomen, the legs on the thighs. The toes were flexed and the arches higher than normal. Any movement caused a shrieking cry as if in pain. There was considerable swelling, which

did not pit on pressure, but there were no redness and no fluctuation. There was discoloration over the middle of the left tibia and the upper part of the right thigh. There was epiphyseal enlargement of all the extremities. There was dorsal scoliosis. On May 12, 1914, the Roentgen-ray report (Fig. 1) showed fracture of the right fibula and femur and the left tibia and long fibula. The femur was very thin in the central third. The epiphyseal ends of the long bones and the tarsal bones showed no definite points of ossification. There was fracture of the radius and ulna, right and left. On July 21, 1914, roentgenograms were taken, which showed a definite amount of lime deposits in lamellae of bones. At the middle of the shafts of the left tibia there was a fracture; at this point there was deficient lime deposit. There was a distinct bowing forward at this point. There was a fracture with callus formation in the upper third of the shaft of the right radius and a similar condition in the ulna of the left arm. A roentgenogram taken Sept. 2, 1914, showed the same findings as before. On Oct. 6, 1914, the patient was getting along well, was gaining in weight and was looking well.

Summary of Roentgen-ray findings showed multiple intraperiosteal fractures of the shaft of the long bones with considerable callus formation. Bones showed little tendency to bend before fracture. There was also evidence of bone absorption at the seat of some of the fractures. There was absence of thickening on the concave side of the long bones; the epiphyseal line, however, was somewhat irregular, an evidence of rachitic changes. At the time of the discharge of the patient from the hospital, five months after she entered, the fractures showed a marked improvement, as evidenced by Figure 2, and the bones showed increased calcium deposit and the bone condition was in the stage of repair.

Fig. 3 (Case 2).—Osteogenesis imperfecta tarda, V. K., aged 3 years.

Case 2.—V. K. was admitted to Cook County Hospital Nov. 28, 1914. The diagnosis was osteogenesis imperfecta tarda. The child was brought to the hospital by the father because the boy was unable to use his arms and legs. The father thought this began about a year before; previously to that he had been able to walk. The child had never been seriously sick at any time. The feeding history of the boy was not obtained.

The family history showed the father and mother living and well. There was another child 2 years of age brought to the hospital at the same time with a similar trouble, which had come on five months before. There were also one child at 4 years and one at 1 month living and well.

Examination showed a poorly nourished boy of 3 years who appeared below par, both mentally and physically. The head was large, appeared slightly hydrocephalic, and the hair was long and silky. The teeth were all present, but poorly formed. There was cervical adenopathy. There was flaring of the chest in the lower portion. A rosary was present, and there were nodules at the seat of the costal fractures. The lung findings and heart findings were

Fig. 4.—Same as shown in Figure 3, at the time of entrance.

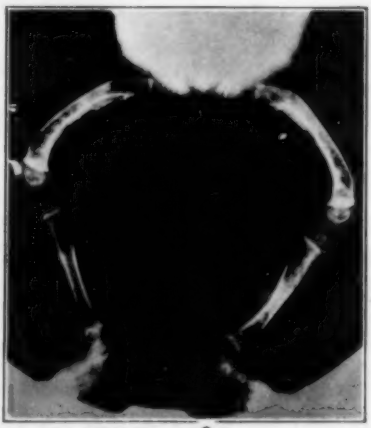

Fig. 5.—Same as is shown in Figure 3 (Case 2), six months after treatment, showing a marked improvement.

negative. There was potbelly. The liver and spleen were negative. The extremities showed marked bend in the lower arm and of the femur. There was enlargement of the epiphyseal end of the femur at the knee. The upper portion of the fibula was freely movable and the shaft appeared to be cartilaginous. Both knee joints were very loose and the tibia could be moved laterally at the knee joint. The movements of the legs were painful. The musculature all over the body was flabby, but there seemed to be no complete loss in motion in any group. The knee jerks were increased.

Roentgenograms of the bones in Case 2 (Fig. 4) show the bones to be of less density than normal, and they appear thin and atrophied. The greatest density is shown subperiosteally in the shafts as a thin, almost paper-like layer, while the medullary cavity seems to be increased at the expense of the spongiosa. The epiphyseal lines are sharp, but perhaps less regular than normal. The concave side of the shafts of the long bones show an absence of thickening, which is usually markedly in evidence in rickets. The fractures are numerous and in most cases occur near the middle of the shafts and show large deposits of callus with little tendency to ossification, although there is a tendency to calcification. The bones as a whole show increased radiability

Fig. 6 (Case 3).—C. S., aged 2 years, osteogenesis imperfecta.

and appear unduly translucent. Some of them appear to have but little increased density over the soft parts. Six months later, while still under treatment, internally as well as by the orthopedic department, the child was again examined by means of the Roentgen ray and the general condition of the bones was greatly improved, as evidenced by Figure 5.

Case 3.—C. S., was admitted to Cook County Hospital Nov. 25, 1915, and died Jan. 9, 1916. The diagnosis was osteogenesis imperfecta tarda with hydrocephalus and secondary rachitic changes, with a complication of bronchopneumonia. There was no history obtained except that the child had always been ill. The father said that the enlargement of the head had been present from birth. The complaint at the time of entrance was loss in weight and poor condition. The father was well and the mother was sick with pneumonia. There were five children, aged 9, 8, 7, and 3 years and one 8 months old, all well. There had been four miscarriages. No feeding history was obtained.

Examination showed an emaciated child of about 2 years, with several bone deformities. The hair was lusterless, uneven, long and fluffy. The head was hydrocephalic, square, with prominent parietal bones, and sweating. The eyes were bulging, pupils equal and reacted to light and accommodation. The mouth contained badly discolored teeth, just appearing through the gums, also an inflammation extending around the entire course of the gums and

tongue. The tongue presented many small spots of ulceration. The thorax showed a rosary on both sides anteriorly; the left thorax was larger than the right. The ribs were bulging on the left side posteriorly. There was kyphosis of the dorsal and lumbar regions, and lordosis of the upper dorsal region. There was potbelly, tympanitic, but no tenderness. All the bones of the extremities were affected. Both femurs showed fractures with a subsequent contraction of both legs and shortening of the hamstring tendons. There was a marked contraction of all the bones of the arms and legs, the clavicles have even seemed to have fractured (three fractures are visible in the roentgenograms). The patellar and Babinski reflexes were positive. Râles were heard throughout the chest; there were no areas of consolidation, no bronchial breathing. The heart tones were rapid, but there were no murmurs.

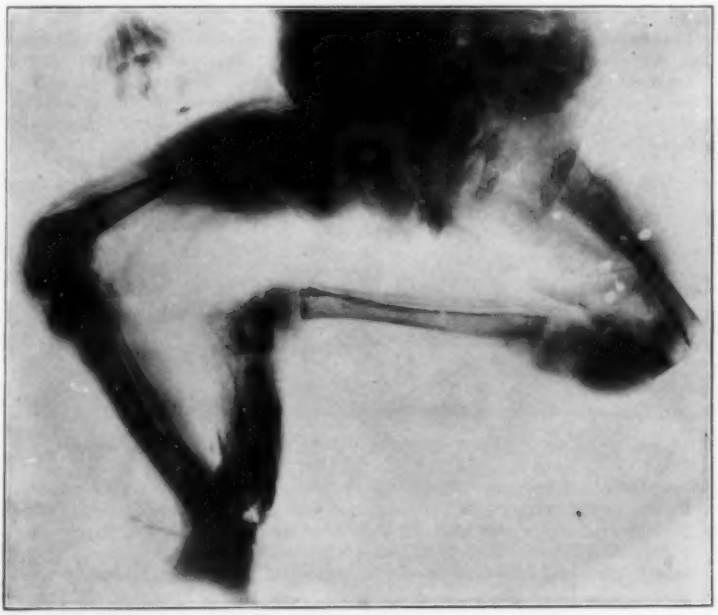

Fig. 7 (Case 3).—C. S., aged 2 years, osteogenesis imperfecta.

The Roentgen-ray findings on Dec. 2, 1915 (Fig. 7), show that the entire bony skeleton of this patient was involved in a high-grade osteo-atrophia; the long bones are very delicate in appearance, comparatively little distinction being noted between cortex and medulla. The former is, however, visible as a thin paper-like layer. The epiphyseal lines are (excepting the wrists) normal. Numerous intraperiosteal fractures are noted, the following bones being involved: left humerus three, left radius one, left ulna one, right humerus two, right ulna one, right radius one, right femur two, right fibula one, left femur one, a total of thirteen fractures. There is a peculiarity at the site of fractures noted which represents a ring of absorption of bone salts, but with definite callus formation surrounding these areas; the spine is seen deflected to the left to the middorsal region. The child died of bronchopneumonia Jan. 9, 1916.

CASE 4.—T. R., aged 3 years (Fig. 8), was admitted to the Cook County Hospital June 8, 1916, on the service of Dr. May Michael. A diagnosis was made of osteogenesis imperfecta tarda, with a bronchopneumonia. The patient is still in the hospital at the time of writing. He has had a cough ever since he was 6 months of age. He was at the Home for Crippled Children one month for advice. The child was born spontaneously at full term at Cook County Hospital, May 9, 1913. The first teeth appeared at 9 months. The child never walked. He was breast fed till nine months before entrance, then mixed diet was given. The family history showed the father and mother to be well; there were three other children, 1, 3 and 6 years of age, respectively, all well. Physical examination showed a poorly developed boy. The head was large, square and of a rachitic type. The eyes, nose and ears were normal. The lips were dry and cracked. The tongue and buccal membranes were sites of stomatitis. The pharynx was red. The chest was of a narrow lateral dimension, showing a rosary and marked flaring costal margins. The lung resonance was normal. There were a few coarse râles over the left lower lobe, but there was no bronchial breathing. The heart was normal. There was potbelly. The liver and spleen were not palpable. The extremities showed enlargement of the epiphyses on both lower and upper. On June 15, 1916, Roentgen-ray findings (Fig. 9) showed the case to be osteogenesis imperfecta and the lungs suggestive of tuberculosis. On June 23, 1916, roentgenograms

Fig. 8 (Case 4).—Osteogenesis imperfecta, T. R., aged 3 years.

showed the chest very narrow and the pulmonary area considerably increased in shadow; this shadow may or may not indicate tuberculosis. Examination of the extremities revealed that the long bones were very narrow as compared with their length; the shadow indicates very delicate bone structure; there is very little distinction between cortex and medulla; multiple fractures are seen to involve practically all of the long bones. A noticeable feature is an absorption of calcium at the seat of fractures. The bones are not curved as in rickets. The epiphyseal lines are more or less negative and differ greatly from the appearance usual in rachitis.

Of the four cases of osteogenesis imperfecta above described, two are of boys and two of girls. Their ages were 16 months, 3, 2 and 3 years, respectively.

DIFFERENTIAL DIAGNOSIS

The Roentgen ray is invaluable in the differential diagnosis of osteogenesis imperfecta, and also chondrodystrophia foetalis, cretinism, mongolism, rachitis, infantile scurvy, syphilis (early congenital and later manifestations) and tuberculosis of bones.

In chondrodystrophia foetalis the trunk is normal, while the

Fig. 9 (Case 4).—Osteogenesis imperfecta, T. R., aged 3 years.

extremities are shortened and deformed. In the skull the clivus is often seen in the lateral position and there is usually malposition of the nasal bones. If the root of the nose is retracted, they are almost horizontal, while if flattened, they are more vertical. The flattening of the bridge of the nose is due either to a primary tribasilar synosteosis or a failure of development, which causes the base of the skull to be shorter. The ribs are thickened at the epiphyseal lines. The extremities are short and thick and the epiphyseal regions prominent.

Fig. 10.—Chondrodystrophia foetalis, N. F., aged 2 years.

Fig. 11.—Radiogram of chondrodystrophia foetalis. Same patient as shown in Figure 10.

The center of the body is displaced upward. The shafts of the bones often show great thickenings and shortening of the cortical substance, and overgrowth of the bony epiphysis is so marked that it often appears to overlap that of the epiphyseal line. The periosteum shows great thickening, the cortical substance is broader and thickened and the medullary canal is narrow, and sometimes the latter is replaced by hard cortical tissue. Thus it will be seen on examination of Figures 10 and 11 that the bone changes are marked in both the length and breadth. "The shortening of the long bones is due to the cartilaginous ossification of the epiphyses, and it is very evident that these abnormalities are brought about by the disturbance in the normal process of ossification in the primary cartilage" (Rotch).

In cretinism the body length is normal at birth, but shows later a greatly retarded development. The degree of retardation varies with

Fig. 12.—Cretin, aged 16 months. On superficial examination it shows some resemblance to osteogenesis imperfecta. However, the Roentgen-ray findings (Fig. 15) make the diagnosis complete.

the degree of thyroid atrophy (directly), and the amount and length of time of treatment. There is a universally retarded development of the bony skeleton due to delayed endochondral and periosteal growth, which is especially marked in the carpal and tarsal bones and in the phalanges. There is delayed development of the bony nuclei in the epiphyses and delayed union between epiphyses and diaphyses. The delays in bone deposits are usually very marked. A 2-year-old child may show bone development of a 6 or 12 month infant.

In mongolism Roentgen-ray examination has no great practical value, as in marked cases clinical diagnosis is easy and the bone changes have no definite pathognomonic characteristics. The general skeletal development shows no pathognomonic changes, the degree of retardation varying in different cases and different regions in the same case, while others may show no retardation. On the whole, the bones are well developed for their age, in fact occasionally the short bones

are developed too early. The skull is usually microbrachycephalic, the orbits low and converge inward, the sella turcica small, with overlapping clinoid processes, which often appear to involve the hypophysis. The hands are short and broad, due to small metacarpal and phalangeal bones. The thumb and little finger show the shortening to the greatest degree. The little fingers often show concavity on the side approximating the ring finger. This is chiefly due to shortening and curving of the middle phalanx. The thumb often shows a button like appearance with circular-like contraction at the proximal end of

Fig. 13.—Mongolian idiot, aged 1 year. See Roentgen-ray findings, Figure 16.

the metacarpal and distal end of the basal phalanx. There is a tendency to congenital anomalies, among which bone deformities are common; clubbed feet, syndactylism, superfluous toes, spina bifida, and micromelia of the upper extremities are often associated with other congenital deformities, as of the heart, genito-urinary tract and ears.

In rickets partial or complete fractures are usual, but they are not intraperiosteal and there seems to be very little tendency toward callus formation, although apparently enough to make the bone more or less solid. The calcium content of the callus is so very low that it is almost invisible in a roentgenogram. Deformities in rickets are much more

Fig. 14.—The Mongolian idiot and cretin, each about 2 years of age, showing the marked difference in physical development between these two conditions.

Fig. 15.—Radiogram of cretin illustrated in Figure 12, showing delayed epiphyseal ossification.

marked in the lower than in the upper extremities. Bowing and bending is characteristic. In the femur the greatest change may be in the neck, causing coxa vara. The pelvis may become flattened and the body shortened as a whole. Not infrequently palpable nodular thickenings involving part of the cortex are seen on the convex surface of the long bones. Increased radiability of bones is a property which rickets in its active stage shares with osteogenesis imperfecta. After the process in rickets subsides the bones, while still showing deformi-

Fig. 16.—Radiogram of Mongolian idiot shown in Figure 13. Normal epiphyseal ossification.

Fig. 17.—Mongolian idiot, showing curving of little fingers.

ties and curvatures, appear broader than normal and show even increased density of bone, which is especially marked at the ends of the diaphyses. The periosteum in rickets is definitely thickened, but the periosteal bone shadow is often pale, due to the low calcium content. The cortex has about the same appearance as in osteogenesis imperfecta. On the concave sides of long bones the cortex is thickened, which is almost pathognomonic of rickets; it may be thinned on the convex side. The medullary cavity is often increased in size in rickets and constantly so in osteogenesis imperfecta. The epiphyses,

which in osteogenesis imperfecta are normal, show most marked changes in rickets. The zone of proliferation is widened, with an irregular, toothed appearance on the epiphyseal side of the diaphysis, and there is also a broadening and flaring out of the epiphyseal end of the diaphysis, which is very characteristic for rickets. The epiphyses tend to be larger than normal, irregular in outline and may be of decreased density. The end of the shaft is streaked and presents an irregular line at the joint end and above it a curious transverse zone of different structure from the rest of the bone.

Fig. 18.—Acute rickets, first stage, showing thickening of cortex, pale spongiosa, cupping and fraying of the ends of the shafts, with poorly developed epiphyses and haziness of joints.

Lovett[26] divides bone lesions of rickets into three stages. As only the severe types of rickets call for differentiation from osteogenesis imperfecta and only from the late type of the latter, we will describe only the severe lesions, as noted by him. In the first stage the epiphyses cast little or no shadow, while the center of ossification is small or absent and at times appears multiple. The diaphysis becomes frayed out, instead of clear cut, the periosteum thickened, and the

26. Lovett: The Roentgenographic Appearances in Rickets, with a Comment on Differential Diagnosis, Jour. Am. Med. Assn., 1915, **65**, 2062.

whole joint appears hazy. Multiple fractures are common. This is the stage which is frequently classed as osteogenesis imperfecta (Fig. 18). In the second stage the shadow of the epiphysis becomes more marked, the area is ragged and irregular, the ends of the diaphysis begin to broaden, especially on the side on which the strain is greater, and here produces a ledge or lip next to the epiphyseal line. There is a thickening on the concave side of the shaft, which is a compensatory

Fig. 19.—Rickets, second stage, showing marked thickening of periosteum, flared and toothed appearance of ends of shafts, with increased bony formation in the nuclei.

change. The diaphysis begins to give a more definite shadow. The ends next to the diaphysis are streaked longitudinally and are the area of maximum disturbance. At the epiphyseal end of the shaft there is generally a transverse area of increased density, reaching about a quarter or half an inch from the epiphyseal line. This continues into the third stage. Further changes in the second stage consist in the chambering of the interior of the bone, where light areas in the shaft

indicate the absence of marked bone deposit, and heavier lines of ossification show the irregular development of trabeculae. The second stage is generally a period of systemic reaction to the disease, in which signs of returning ossification occur and when deformity begins (Fig. 19). In the third stage, the epiphysis begins to resume its normal contour and homogeneous shadow density. Irregularities persist in the marginal outline, and there is still a little mottling in the ossification. The lipping of the diaphyses has enlarged the bone ends, and

Fig. 20.—Rickets, third stage. Shafts show marked and irregular thickening, periosteum thickened on the concave side, disappearance of flaring and irregularities at the ends of the shafts and epiphyses distinctly ossified; marked curvature of the shafts.

there is in consequence a discrepancy in breadth between the diameters of the diaphysis near the epiphyseal line and the epiphysis (Fig. 20).

In infantile scurvy the most constant finding is an irregularly circumscribed shadow of varying diameter and intensity at the end of the diaphysis at the seat of new bone formation. This shadow, according to Rehn[27] enables one to make an early diagnosis of scurvy when all

27. Rehn: Röntgenaufnahmen von mit Lues congenita und Rachitis affizierten Knochen, Naturforscherversammlung, Düsseldorf, 1898.

other classical clinical signs of scurvy are absent, provided it is possible to exclude congenital syphilis. Less constant than this shadow are the subperiosteal shadows at the seat of hemorrhages. These shadows may be invisible even at the height of hemorrhage, becoming more and more distinct with age, probably due to the deposit of osteophytes. Fractures and infractions are demonstrable in scurvy. Other findings in scurvy, which, however, are not always demonstrable by Roentgen rays, are epiphyseal separation and displacements, hemor-

Fig. 21.—Infantile scurvy, showing bone atrophy, periosteal disturbance in shaft and so-called white line at the end of the shaft. This case also presents marked rachitic changes.

rhages within the joint capsule (considered to be very rare by Reyher,[28]) and occasionally, but rarely, intramuscular hemorrhages may be demonstrated. The clinical symptoms often enable one to make a diagnosis of scurvy and, according to Frangenheim,[6] especially in older children a diagnostic triad makes diagnosis comparatively easy;

28. Reyher: Das Röntgenverfahren in der Kinderheilkunde, Meusser, Berlin, 1912.

(1) hemorrhagic diathesis, which is manifested by tendency to hemorrhages and multiple hemorrhages anywhere in the body, with its sequela, marked anemia; (2) severe pain in extremities accompanying every movement; (3) swelling of the joints. From these signs multiple subperiosteal hemorrhages are pathognomonic.

In syphilis we must distinguish between the early congenital (Fig. 23) and the later bone changes (Figs. 24 and 25). As to the diagnosis of syphilitic lesions of the bones, Fraenkel[29] says: "If in an infant in its first weeks of life we find roentgenologically at the epiphyseal line either homogeneous transverse shadow or a streak interrupted by lighter transverse streaks, the epiphyseal line being well outlined

Fig. 22.—Infantile scurvy, showing epiphyseal separation or displacement due to hemorrhage into the joint.

toward the diaphysis, and toward epiphysis a serrated ribbon-like shadow, we have a positive proof of existence of osteochondritis syphilitica" (See our case, Figure 23). In early congenital syphilis the entire skeletal system is affected, the long bones suffering chiefly. In later manifestations, in which periostitis ossificans is a very important finding, we see newly formed subperiosteal bony masses with bony structure. They are most marked in the middle of the diaphysis of the femur and less marked in other long bones. Old cortex may often be differentiated from the newly formed subperiosteal bony masses. Cortical thickening is therefore an important point in dif-

29. **Fraenkel: Die Röntgendiagnose der kongenitalen Knochensyphilis, Vortrag geh. auf dem VII. Kongress der deutschen Röntgen gesellschaft, Berlin, 1911.**

ferential diagnosis from osteogenesis imperfecta, in which disease the cortex is always very thin. In the phalanges the epiphyseal line is somewhat lighter, the diaphysis is stronger and more compact and forms a dark, sharply circumscribed shadow. The phalanges are longer and thickened. There are definite changes in the exterior of the bone without any change in the interior, unless suppuration has taken place and other long bones of the body are similarly affected, which differentiates syphilitic dactylitis from tuberculous dactylitis. Fractures are comparatively rare in syphilitic infants (Lovett[26]).

Fig. 23.—Early congenital syphilis, showing marked changes throughout the entire bone structure.

A characteristic of tuberculous lesions is primarily and definitely a destructive local process, without evidence of a tendency to bone stimulation. Osteogenesis, on the other hand, appears to be a general atrophy of all the bones of the body. In tuberculosis light shadows, due to bone destruction and calcium absorption, are seen surrounded by otherwise normal dark bone shadows (Fig. 26), while in osteogenesis all the bones of the body show more uniformly increased permeability to Roentgen rays. The neighboring bone areas show

atrophy, the cortical substance is thinned and the spongy portion appears less dense, often giving a shadow of a density but little greater than the soft tissues. Callus formation in tuberculosis is very deficient. When tuberculosis affects joints, there is a high-grade atrophy and destruction of the bone. The bone ends show marked transparency. This increases the nearer it approaches the joint (Reyher[28]), thereby decreasing and often impairing the visibility of the joint contour. The entire region of the joint may become less visible. Comparison should be made with the well side, especially early in the disease, when diagnosis may be difficult. The tuberculous joint lesions

Fig. 24.—Late bone changes in congenital syphilis.

and fractures are very painful, thus differing from fractures of osteogenesis imperfecta, which seem to be attended with but little pain.

Osteomyelitis presents an outline showing periosteal reaction in the form of proliferation of new bone about the necrosed area, or again the sequestra may be plainly visible (Fig. 27). It is difficult to make positive diagnosis before the second week. By the second week we have evidence of a more or less marked periosteal proliferation and new periosteal bone formation about the necrosed area. Light and irregular shadows at the seat of the bone involvement are also now visible, due to bone destruction. Later in the disease distinct bone sequestra surrounded by a definitely lighter shadow are characteristic.

Before concluding our discussion we desire to point out the tendency on the part of Cases 1 and 4 of our series to develop secondary rachitic bone lesions. These rachitic changes led to a questionable diagnosis in two of our cases; however, a brief review of the changes characteristic of the two conditions will, I believe, clear up the situation. The combination of the two conditions in the late form of the

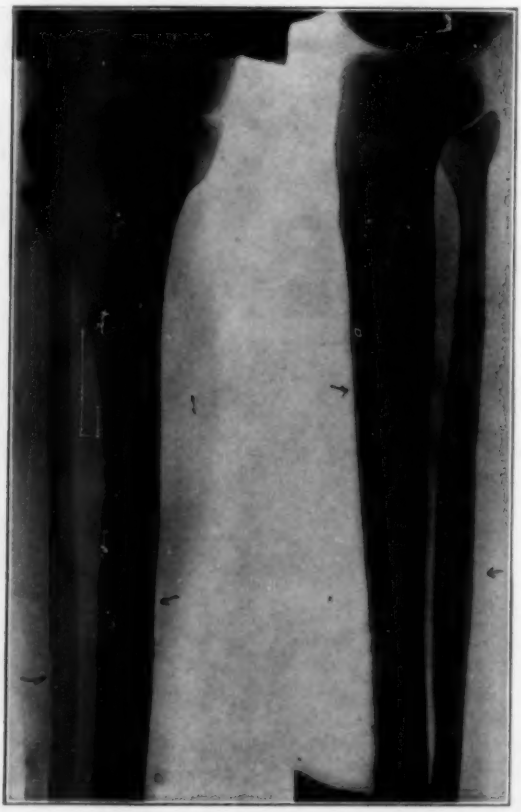

Fig. 25.—Congenital syphilis with later bone changes of periostitis ossificans.

disease is the rule rather than the exception, while the early congenital type has not infrequently been described as fetal rickets.

Most of the cases are sent into the wards as scorbutus, because of the pain at the seat of the fractures following motion of the extremities; the roentgenograms, however, readily show the cause of the pain.

Segawa[15] describes for the first time the combination of osteogenesis imperfecta as a congenital affection with Barlow's disease and rickets as acquired affections in an infant. The former was diagnosed clinically, the latter two only anatomically.

PROGNOSIS

The prognosis for infants affected with osteogenesis imperfecta is not favorable. A great majority of these children are stillborn or they die a short time after birth or within the first three years of their

Fig. 26.—Tuberculosis of the bones.

life. Since the disease is caused by a congenital anomaly, prognosis depends on the intensity of this anomaly, which may be judged from the time of its appearance and other clinical symptoms. Besides, these children are very susceptible to secondary infections and they usually die of some intercurrent disease. Prognosis is more favorable for cases occurring later in childhood as some seem to undergo spontaneous cure.

In the treatment of the disease calcium salts, phosphorus, and cod liver oil should be given a thorough trial. We have seen but little result from the use of desiccated thyroid parathyroid thymus, supra-

renal, anterior lobe of the pituitary gland and pineal gland, which have all been tried alone and in combination in our cases. Joachimsthal[30] reports a case in which by administration of phosphorus preparations he was able to produce within three months an almost normal

Fig. 27.—Osteomyelitis.

formation of bones and so complete healing of fracture that roentgenograms taken after that time showed no traces of the disease. Immobilization, with moderate extension of the fractures by casts, prophylaxis against further fracture, fresh air and sunshine, when

30. Joachimsthal: Heilungsvorgänge bei Osteogenesis imperfecta, München. med. Wchnschr., 1912, Part 1, **59**, 1246.

combined with cod liver oil, phosphorus and the calcium salts together with a diet containing fresh fruits and vegetables have resulted in most striking results in our cases of osteogenesis imperfecta tarda.[31]

	gm. or c.c.
℞ Phosphori	0.01
Olei morrhuae	60.
M. Sig.: 4 c.c. twice daily or	gm. or c.c.
Calcii phosphoric. tribasic. puriss.	6.
Olei morrhuae	60.

M. Sig.: 4 c.c. twice daily.

5514 Indiana Avenue.

31. In addition to the references already given, the following will be found of interest:

Dieterle: Die Athyreosis unter besonderer Berücksichtigung der dabei auftretenden Skelettveranderungen, sowie der differentialdiagnostisch vornehmlich in Betracht kommenden Stöungen des Knochenwachstums, Virchows Arch. f. path. Anat., 1906, **184,** 915.

Lovett and Nichols: Osteogenesis imperfecta, Brit. Med. Jour., 1906, **2,** 915.

Sumita: Beitrag zur Lehre von der Chondodystrophia foetalis (Kaufman) und Osteogenesis imperfecta (Vrolik) mit besonderer Berücksichtigung der anatomischen und klinischen differentialdiagnose, Deutsch. Ztschr. f. klin. Chir., 1910, **107,** 1-111.

Fraenkel and Lorey: Die Rachitis im Röntgenbild, Supplement 22, der Fortschrift a. d. Geb. d. Röntgenstr., Hamburg, 1910, Suppl. 22, p. 5, Lucas Gräfe and Sellen.

Simmons: Osteogenesis imperfecta und idiopathische Knochenbruchigkeit, publication of the Massachusetts General Hospital, Boston, 1908, **2,** 17.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

WITH REPORT OF THREE FAMILIES AND A REVIEW OF THOSE PREVIOUSLY RECORDED *

WALTER R. STEINER, M.D.
Visiting Physician, the Hartford Hospital
HARTFORD, CONN.

In 1865 Babbington[1] reported an interesting family in which recurring epistaxis had been observed for five generations. The transmission was through both male and female, but no mention was made of telangiectases in any of them. The first family in which these telangiectases were found was reported eleven years later by Legg,[2] who described numerous small nevi on the face, forehead and trunk of his patient. They developed about his 41st year. These cases were followed by others reported by Chiari,[3] Rendu,[4] Osler,[5] Josserand,[6] Kelly,[7] Hawthorne,[8] Parkes-Weber,[9] Phillips,[10] Waggett[11] and Ballantyne.[12] Rendu, however, was the first of these observers to associate the presence of epistaxis with multiple telangiectases as clinical manifestations of a distinct morbid entity. Henceforth the erroneous diagnoses of hemophilia, acquired angiomas from cirrhosis of the liver and hemorrhagic diathesis were no longer applied to this condition. Further interest in its study was aroused by the papers of Sir William Osler, whose first published article on it appeared in 1901. Most of these cases were carefully abstracted in 1909 by Hanes[13] when he reviewed the literature on this subject and accurately described two

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*Read in part at the meeting of the American Climatological and Clinical Association, Washington, D. C., May 9, 1916.

1. Babbington: Lancet, London, 1865, **2,** 362. Recently Lane (Jour. of Heredity, 1916, **7,** 132) has described hereditary nosebleed observed in a family for three generations.
2. Legg: Lancet, London, 1876, **2,** 856.
3. Chiari: Erfahrungen auf dem Gebiete der Hals und Nasenkrankheiten, Vienna, 1887, p. 60.
4. Rendu: Gaz. d. hôp., 1896, **49,** 1322.
5. Osler: Bull. Johns Hopkins Hosp., 1901, **12,** 333.
6. Josserand: Bull. de la Soc. méd. d. hôp. de Lyon, 1902, **1,** 244.
7. Kelly: Glasgow Med. Jour., 1906, **65,** 411.
8. Hawthorne: Lancet, London, 1906, **1,** 90.
9. Parkes-Weber: Lancet, London, 1907, **2,** 160.
10. Phillips: Proc. Roy. Soc. Med., 1908, **1,** Laryngological Section, p. 45.
11. Waggett: Proc. Roy. Soc. Med., 1908, **1,** Laryngological Section, p. 70.
12. Ballantyne: Glasgow Med. Jour., 1908, **70,** 256.
13. Hanes: Bull. Johns Hopkins Hosp., 1909, **20,** 63.

additional families, so that fifteen were then reported.[14] Since then eleven more families have been described, including the three here detailed, so that this condition has now been found to exist in twenty-eight families.[15] Other, isolated, instances, with no further cases in any of their families, have been reported by Chauffard,[16] Kelly,[17] Fox,[18] Galloway,[19] Lack[20] and Adamson,[21] but I have omitted all consideration of them on account of their lack of any hereditary tendency toward this condition.

It has been defined as a hereditary affection, manifesting itself in localized dilatations of capillaries and venules, forming distinct groups or telangiectases, which occur especially on the skin of the face, nasal and buccal mucous membranes and give rise to profuse hemorrhage, either spontaneously or as the result of trauma (Hanes).

In its causation, a hereditary tendency is the only factor which is constantly present, although others, such as syphilis, alcohol and traumatisms, have been irregularly reported. A history of syphilis, however, is only recorded in three instances, yet its unrecognized presence may probably have existed in a somewhat greater frequency. Stokes[22] recently has written an interesting article showing that syphilis, chronic plumbism, hyperthyroidism and nephritis may cause cardiovascular degenerative conditions which result in the formation of generalized telangiectasia. Alcohol, likewise, is a most inconstant factor, which is only thrice stated to have been present, and traumatism, of etiologic importance, is just as rarely seen, for it appears but two times in the histories of the twenty-eight families exhibiting this condition, although

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14. In this enumeration the family reported by Josserand was unintentially omitted and Osler's second case seemed to be an isolated instance, not of the family type. Later another member of the family, similarly affected, was discovered. Gottheil's family was also omitted from Hanes' list. It was published shortly before Hanes' article appeared. Hanes' list includes Babbington's family, in which epistaxis was observed for five generations, but no mention is made of telangiectases in any of its members. It probably should be added to this group, but, on account of the absence of positive evidence, I have omitted it.

15. Laffont: Presse méd., 1909, **17,** 763. Langmead: Proc. Roy. Soc. Med., 1910, **3,** Clinical Section, p. 109. Audry: Rev. de méd., 1911, **30,** 22. Osler: Riforma med., 1911, **27,** 57. Van Wagenen: Med. Rec., New York, 1912, **81,** 109. Sequeira: Proc. Roy. Soc. Med., 1912-1913, **6,** Dermatologic Section, p. 128. Gjessing: Hospitalstidende, 1915, **8,** 1151. Hutchison and Oliver: Brit. Med. Jour., 1916, **9,** 67.

16. Chauffard: Bull. et mém. Soc. méd. d. hôp. de Paris, 1896, **13,** Series 3, p. 352.

17. Kelly: Proc. Roy. Soc. Med., 1908, **1,** Laryngological Section, p. 45.

18. Fox: Brit. Jour. Dermat., 1908, **20,** 145.

19. Galloway: Proc. Roy. Soc. Med., 1910-1911, **4,** Clinical Section, p. 42.

20. Lack: Jour. Laryngol., 1909, **24,** 185.

21. Adamson: Brit. Jour. Dermat., 1909, **21,** 219.

22. Stokes: Am. Jour. Med. Sc., 1915, **149,** 669.

it must be stated, as Hanes has previously shown, that the telangiectases are generally located at points most subject to frequent slight traumatisms. The bleeding in these cases is often so severe that a condition of marked anemia is induced, which may be an important factor in the development of the telangiectases. Certain it is that the bleeding generally precedes the formation of these localized dilatations of the capillaries and venules, and may do so with many years intervening between them. In some of the cases, also, a respite from the bleeding appears to be coincident with the disappearance of the telangiectases. Cases have been reported in England, France, Germany, Denmark and the United States. The Anglo-Germanic race has furnished most of the examples, followed by the Latin and Scandinavian.

Kelly thinks that October to May, inclusive, are the months in which the bleeding is most apt to occur, but other observers have not corroborated this fact. Hutchison and Oliver thought their patient bled more during the summer months. It has been noted in ninety-two males and seventy-three females, so its distribution among the sexes is probably about equal. Both sexes are able to transmit it. In the published cases thirty-two women have transmitted the tendency as against thirty-five men. The pathology of this condition has been investigated on three occasions. The first case was when Dr. Mabel Austin examined at Dr. Osler's suggestion a section of the nasal mucous membrane of a patient, in the first family which Dr. Osler reported. This patient was the first to come to necropsy, which revealed "cancer of the stomach, mesentery and omentum, liver, retroperitoneal glands, lungs and brain." In the stomach there were also found "a dozen round foci, each from 3 mm. to 4 mm. in size, which at first looked like ecchymoses, but were dilated venules and capillaries." The sections of the septum of the nose showed large dilated veins just beneath the epithelium. Our information from the second case comes from a biopsy which Dr. Hanes performed on one of his patients. The tissue was removed from a telangiectatic spot and showed "the obliteration of the papillae of the corium, together with the absence of the usual undulations of the stratum germinativum. This is doubtless due to the relatively enormous dilatation of the blood vessels of the corium, which are seen as wide spaces, lined by a single layer of endothelium lying immediately subjacent to the greatly attenuated epidermis. These dilated vessels can be traced well down into the subcutaneous fatty tissue. A study of sections stained by various special methods failed to reveal any muscular or elastic tissue in the walls of the dilated superficial vessels, although the less dilated vessels in the subcutaneous fatty tissue show the normal arrangement of the tunicae." Consequently, Hanes refers to the insufficient protection of the dilated vessels and

states that it is not surprising that trivial traumatisms produce marked hemorrhage.

In one member of the family reported by Gjessing a microscopic examination was made from an angioma on the left cheek. In the corium blood-filled cavities were found, surrounded by a single layer of endothelium and a thin stratum of connective tissue, devoid of elastic or smooth muscle fibers. In some places the cavities extend upward to the epidermis, where the papillae were flattened. In one spot the cavity extended down into the subcutaneous tissue, where, in the surrounding area, numerous well-developed hair follicles and sebaceous glands were seen. In this situation the elastic fibers were as numerous and well developed as in normal tissue. The changes then consist in a dilatation of the capillaries of the small veins, with the formation of telangiectases of the three types which I shall later describe. These dilated vessels, being only lined by endothelium without the additional presence of elastic or muscle fibers, become consequently very liable to rupture, induced either spontaneusly or by trauma.

The chief symptom is hemorrhage, which may come from the telangiectases in the nose as an epistaxis or from those situated elsewhere. These locations are the conjunctivae of the upper and lower lids, the ears, cheeks, nose, lips, mucous membranes of the mouth in the region of the hard or soft palate, the uvula, buccal mucous membranes or gums, tongue, neck, trunk, back, arms, finger tips, under the nails, or on the feet. The bleeding varies greatly in frequency. It may occur three to four times daily, once or twice a week or even with a greater interval of freedom. Kelly has described a patient in whom it was most apt to take place between the months of October and March, and would be both profuse and frequent. The amount of blood lost also varies greatly. In Kelly's patient, just referred to, it was so marked that death from syncope finally resulted. Legg and Chiari have reported cases in which dropsy ensuing from loss of blood caused a fatal termination, while Phillips has recorded a case in which death came from hemorrhage of the gums. Chiari also mentions a child, in one of his families, who died from a severe nosebleed, and Gottheil speaks of a male dying from the same cause.

The bleeding may be a slight trickle from the nose or the spots, or come with more force. One of Hanes' patients found it not uncommon for him to injure one of the lingual telangiectases while eating, so that the blood would actually spurt from the injured spot and render further progress with the meal impossible. Gottheil has described two varieties of bleeding in one of his cases. From the nose it occurred as a slow trickling, lasting perhaps ten or fifteen minutes, while from the visible lesions of the tongue and lips it came as a sudden projectile spurt,

sometimes reaching out a foot or two, if on the lips, or if his mouth was open, and stopping spontaneously in two or three minutes. Langmaid speaks of his patient as suffering for about twenty years from frequent epistaxis and adds that occasionally his face or tongue has burst out bleeding. Legg also speaks of the bleeding from the spots as being frequently spontaneous in origin in his case, but generally in all the instances it is the result of traumatism, while the hemorrhage from the nose is spontaneous in its onset.

Less severe bleeding has produced, by the resulting anemia, vertigo, headaches, weakness, dyspnea on exertion, palpitation and swelling of the ankles. In one instance fainting was induced after a prolonged epistaxis, while another patient, depleted from the hemorrhages, finally came down with an endocarditis. The prostration from this cause prevented another from working for about three years. The onset of the epistaxis is generally in early childhood, but the attacks become more severe and prolonged as the patients advance in years, the period between the 35th to 38th years being the time when the increase is especially noted. The telangiectases seen in this condition are of three varieties: the pinpoint, which is most apt to be seen on the skin of the hands and face, and which may be readily overlooked; the spider form, which is the most common and which Parkes-Weber prefers to call spider angiomas rather than spider nevi; and the nodular type, which may originate in the center of a spider angioma and finally form a solid vascular tumor, split pea in size. They are most frequently seen on the nasal and buccal mucous membranes and on the mucocutaneous junction of the lips, but may be found in the other locations mentioned above. They begin as capillary dilatations and are bright red in color. Later the venules give the cutaneous telangiectases a violaceous or purple color by participating in their formation. The spots on the mucous membranes, however, always remain a bright red. They may be seen early in life, for Hanes has observed them in a boy of 8 years, but generally, if present at such an age, they are not especially numerous, for they do not attain their full number until after the age of 35. Even then they appear and disappear with marked frequency and seem to bear some relation to the bleeding, being less marked if a considerable respite from hemorrhages is observed. Parkes-Weber speaks of a vicious circle being established by the repeated attacks of bleeding giving rise to a grave condition of anemia, which in its turn increases the tendency to hemorrhage.

In Parkes-Weber's case a small patch of chorioretinitis was found in an examination of the fundus of the right eye by the ophthalmoscope, while in Sequeira's case the retinal vessels were thickened, but there were no hemorrhages.

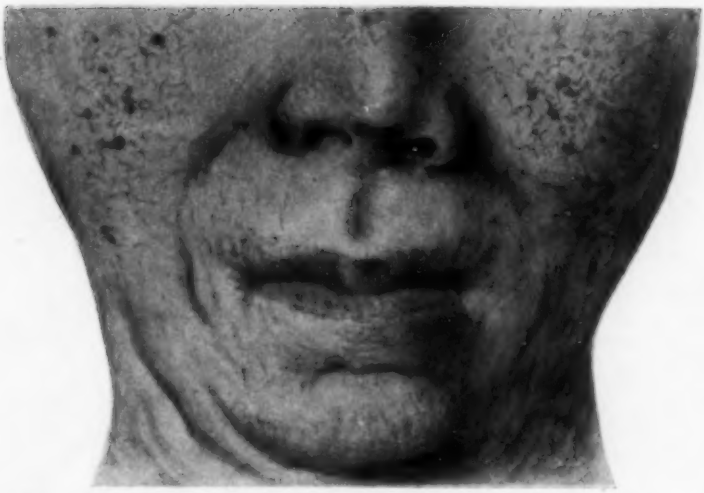

Fig. 1.—Telangiectases on the face. The family tree of this patient is given in Figure 3 (Family 28, Steiner 1, III, 22).

Fig. 2.—Telangiectases on the tongue. The family tree of this patient is given in Figure 3 (Family 26, Steiner 1, IV, 12).

Before Rendu's time the disease was generally considered hemophilia. Chiari, however, caught a glimmer of the real truth when he first diagnosed the condition as one of telangiectases of the mucous membranes, which were hereditary in a family. Unfortunately, after a further study of his cases, he regarded the affection as due to hemophilia. The epistaxis, or the telangiectases, may exist alone in certain members of the families implicated, but the hereditary tendency in them and the finding of the cardinal symptoms combined in other members of the family will make the diagnosis simple. The fact that the females are not affected by hemophilia may be, at times, of diagnostic value.

The outlook is generally not very promising, for the hemorrhages are apt to increase in severity as middle life is reached, when the telangiectases are frequently first seen. In one of the cases, however, there was a cessation of the bleeding as this period was approached, while another bled only after this time from her nose and the telangiectases elsewhere, at each menstrual period. In four out of the 191 cases death has been directly attributed to the hemorrhages, in others it has involved much invalidism, while a third and smaller group has not been much incapacitated by them.

Rendu used with excellent result, in his case, an application on the nasal mucous membrane of a powder of antipyrin, tannin and powdered sugar, and Coe has reported on the beneficial employment of calcium lactate and iron in his case, which he published as one of hemophilia. It is hard, however, to see the rationale of this treatment, for the disease is due to a developmental defect in the blood vessels and measures to increase the coagulability of the blood ought not to yield good results. The use of iron and the application of the thermocautery to many of the spots might more reasonably explain the patients' improvement. A bead of chromic acid, fused on a probe, was used with excellent success by Hanes, who recommends the method highly, as the action of the caustic may be checked at any time by the application of an alkali. The repeated use of this method may be necessary to check the bleeding. After the cause is thus removed, the use of iron and arsenic for the treatment of anemia is indicated. Although it has been unsuccessful in some cases, the cauterization of the troublesome bleeding areas appears to be the most satisfactory form of treatment. The use of radium for the nodular telangiectases might also be of avail.

Since my interest was aroused in this condition from a case on the services of Sir William Osler, at the Johns Hopkins Hospital, in 1899, I have seen instances of it in three families and can give the following partial rehearsal of their histories.

FAMILY 26 (Figs. 1, 2 and 3, Steiner 1, 1916).—Recurring hemorrhages occurred in five generations and twenty-one members of one family; telangiectases were observed in five of them.

F. G., aged 42 years (Hospital No. 66559), was admitted to the Hartford Hospital Feb. 23, 1913, complaining of weakness, shortness of breath and frequent nosebleed (Fig. 3, III, 4).

Family History: The patient's grandfather (Fig. 3, I, 1) was a bleeder, as well as his father (II, 1) and one aunt (II, 6) all of whom are now dead. Of the aunt's family of ten children, two sons (III, 12 and 14) and two daughters (III, 22 and 24) are bleeders. One of the daughters (III, 22, Figs. 1 and 3) has a girl (IV, 18) who is also a bleeder, and one son (III, 12) has two daughters (IV, 10 and 12) and a son (IV, 17) who bleed likewise. One of these daughters, both of whom are married, has a daughter (V, 6) who bleeds from the nose. The histories of III, 22 and IV, 12 (Figs. 1, 2 and 3) will be given later. Another aunt (II, 8) has two sons (III, 29 and 30) who are subject to epistaxis, and an uncle (II, 3) has likewise two sons (III, 6 and 7) who suffer from the same difficulty. The patient (III, 4) has three sons and a daughter (IV, 1, 2, 3 and 4) who are similarly affected.

Present Illness: The patient was in excellent health until he was 14 years old, when he began to suffer from frequent attacks of epistaxis, which were exceedingly difficult to control. They recurred weekly or at more frequent intervals. When he was 16 years old, he had a slight hemorrhage from a small red spot on his face, which was readily checked. Three years later he entered the Prussian army and suffered frequently from the symptoms mentioned above, although the amount of blood lost was never very great. There was never any additional hemorrhage noted from his mouth or rectum, and his urine never contained blood. He remained in a stationary condition during the four years he served in the army and in this period was observed by army physicians and others who told him the bleeding could not be checked. At the expiration of his army service he emigrated to the United States, where he was frequently in very straightened circumstances. Occasionally he found employment in the Hartford coal yards. After two years he returned to Germany again, where he labored successfully for thirteen years as a grocer and lumberman. Then meeting reverses, he came to this country again, four years ago, and has since worked as a pedler. During all this time he has had frequent attacks of epistaxis and has gradually grown weaker. For the past year dyspnea on exertion as well as palpitation have been troublesome symptoms. The hemorrhages generally occur in the mornings and of late have been observed daily. His appetite has been good. There have been no digestive disturbances. His bowels have been constipated, but have recently been moved daily by medication. Of late years he has suffered from hemorrhoids, which occasionally bleed somewhat. He had measles when he was a child. He denies venereal disease. He has been a moderate smoker and drinker.

Physical Examination: The patient was a well-nourished, well-developed Jew. The lungs were negative on examination, but the heart, which was not enlarged, revealed a soft systolic murmur at the apex, which was not transmitted outward, but was heard with increasing intensity on passing upward, being loudest at the base, in the pulmonic area, where the second sound was slightly accentuated. Over both cheeks, on either side of the nose, numerous angiomas are seen, varying in size from pinpoint to one which measures 3 by 4 mm. in size, located 20 mm. below a midline drawn perpendicularly from the left lower eyelid. Two pinhead angiomas are also seen on the nose, and on the mucous membrane of the lower lip ten more are noted from pinpoint to pinhead in size. On the tip of the tongue, two are also observed, the larger measuring 2 by 2 mm., while the smaller resembles a pinhead. Back of the wisdom tooth, on the right lower jaw, there is also one of a similar size, as well as on the buccal mucous membranes and on the posterior aspect of the tongue. Two small ones are likewise seen on the anterior aspect of the helix of the

right ear, while six more are visible on the posterior surface. On the septum of the nose, as well as on the left inferior turbinate, similar angiomas are observed and some of them appear to have bled very recently. The mucous membranes of the nose as well as the conjunctivae are very pale in color.

Blood examination showed red blood corpuscles 4,696,000; leukocytes 4,800; hemoglobin (Dare) 60 per cent.; coagulation time three and a half minutes (Biffi Brook's instrument). A differential count of 300 leukocytes gave polymorphonuclears, 61 per cent.; lymphocytes, 26 per cent.; large mononuclears and transitionals, 12 per cent., and eosinophils, 1 per cent. There were no myeloblasts, no normoblasts or megaloblasts, no poikilocytosis, and but slight anisocytosis. The urine examination was negative. On March 5 Dr. E. Terry Smith examined the patient's nose and observed the presence of an old atrophic rhinitis. He also noted some telangiectases on the septum and left inferior turbinate, which he cauterized on two separate occasions. His other treatment consisted in the use of rest, iron and arsenic. Three days before discharge the patient's hemoglobin was 70 per cent., but the blood examination otherwise showed no change. On April 19 he was seen with me by Sir William Osler, who confirmed the diagnosis. He was discharged from the hospital March 23.

The patient was then lost track of by me and could not be traced, as he had moved from the residence he gave, until April 1, 1916, when he walked into my office. After leaving the hospital he had worked steadily as a pedler until recently, when the hemorrhages from the telangiectases on his face, tongue and nose prostrated him so severely that he found himself in a very much weakened condition and unable to work. A few days later I had a Wassermann and luetin test performed on him, with negative results in both instances. The internal administration of iron chlorid has yielded him some improvement.

Mrs. A. T., aged 33 years (Figs. 1 and 3, III, 24), first seen by me at my office on March 20, 1909, complained of bleeding from the face. The family history is given in the recital of the history of the previous case. The past history shows typhoid fever when the patient was 24 years old, of nine weeks' duration, with complete recovery. Two years previously she injured her thigh severely in an explosion. Her menses have been regular, occurring every twenty-eight days, with a duration varying from three to seven days and with slight pain. She has been married for ten years and has had three children, the age of the eldest being 8 and of the youngest 3. The labors have been instrumental and difficult.

Present Illness: She has bled from the nose ever since she can remember. The epistaxis begins and stops spontaneously. The intervals between the bleedings have varied from three to four weeks up to two or three months. One year ago ergot internally seemed to check them. At this time she first began to bleed from the tongue, pharynx and hard palate. These hemorrhages are also well controlled by ergot and the local application of tincture of ferric chlorid. Ten days ago the bleeding began to be more profuse and would come on especially during eating, when mastication would frequently remove a clot from the tongue.

Physical Examination: The patient was a well-nourished, well-built woman. The lips and mucous membranes were quite pale in color. The tongue was clean. On the dorsum of the tongue, near its middle aspect and slightly to the right, was a raised nodular angioma, split pea in size, with a flattened summit, from the center of which a pinpoint opening of a blood vessel was seen. The mucous membranes of the hard palate showed a number of telangiectases, pinhead in size. They were also seen about the vicinity of the cheek bones, one on the left side of the nose to the right of the bridge and 1.5 cm. from the tip being of the nodular type and split pea in size. The others varied from pinpoint to pinhead in size. All were bright red in color and did not blanch on pressure. On the right hand, near the styloid process, was seen a spot pinhead in size. The heart revealed a soft systolic murmur at the apex,

which is not transmitted outward and was heard with increasing intensity on passing upward, being loudest at the pulmonic area. There was a soft systolic murmur in the vessels of the neck.

Blood examination showed red blood corpuscles, 4,304,000; leukocytes, 7,750; hemoglobin (Dare), 55 per cent.; blood platelets (Pratt's method), 204,788; coagulation time (Biffi-Brook's method), two minutes. Differential count of 500 leukocytes gave polymorphonuclears, 61.8 per cent.; lymphocytes, 26 per cent.; large mononuclears and transitionals, 9 per cent.; eosinophils, 2 per cent., and mast cells, 0.4 per cent. There were no myeloblasts, no normoblasts or megaloblasts, no poikilocytosis, and but slight anisocytosis.

Subsequently the bleeding increased in severity and frequency so that the patient has occasionally been much prostrated by the secondary anemia thus induced. The use of rest, iron and arsenic has been of little avail.

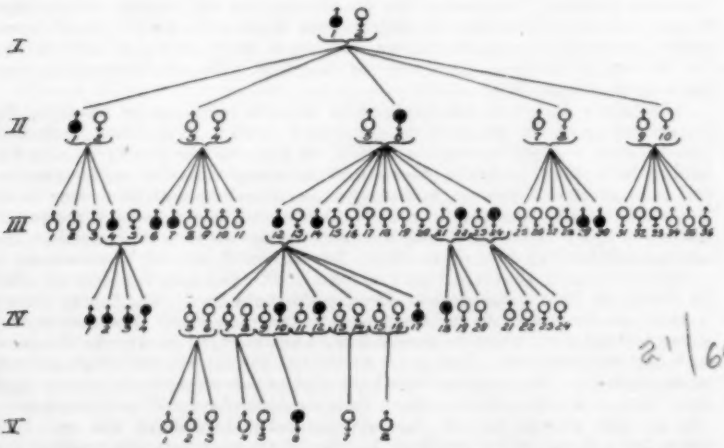

Fig. 3.—Family 26, Steiner 1. The heavily shaded characters in this and all succeeding figures indicate the members of the family affected, while the Roman numerals at the margin indicate the successive generations.

Mrs. D. E., aged 25 years (Figs. 2 and 3, IV, 12), was first seen by me at my office on April 26, 1909, complaining of bleeding from the nose. The family history is given in the recital of the history of the first case. The past history shows influenza every winter ever since she can remember. She had brain fever when very young and measles when she was a child. Her menses began at 14 and were regular every twenty-eight days until five or six years ago, since which time they have come a few days more frequently. She has much pain during the first two days.

Present Illness: Nine years ago she first began to bleed from the nose. The hemorrhages have come on since then five or six times a day, sometimes once a week or more rarely once a month, occasionally there is a two or three month interval. A little worry or excitement will generally bring on an attack, which frequently lasts five or ten minutes. She has never used anything to check the hemorrhages except cold water. Last summer she first began to bleed from the tongue and has bled thus about five times in all.

Physical Examination: The patient was a well-nourished, well-built woman. The lips and mucous membranes were of good color. Over the cheeks, chin, mucous membrane of the lower lip and the tongue were telangiectases varying

in size from a pinhead to split pea in size of which there were two on the tongue which were slightly raised. Some were of the spider type. All were cherry red in color. The heart was negative on examination. A Wassermann reaction on the blood and spinal fluid was later performed with negative results. Blood examination showed red blood corpuscles 4,000,000, white blood corpuscles 10,000, hemoglobin 75 per cent. The urine examination was negative. Subsequently the bleeding, especially from the nose, has increased in severity. The cauterization of the bleeding areas has been of little avail.

FAMILY 27 (Fig. 4) (Steiner 2).—Recurring epistaxis occurred in three members of the family for two generations; telangiectases with epistaxis were present in the only member of the family seen.

E. N., aged 41 years (Hospital No. 66927), was admitted to the Hartford Hospital on my medical service, March 17, 1913, complaining of being run down (Fig. 4, II, 8).

Family History: Her father had died of old age, her mother of pneumonia. Of her four sisters and one brother, one, a sister (II, 5), aged 47, had been subject to attacks of epistaxis all her life, but especially during childhood. She is married but has no children. She resides in Stockholm, Sweden. Another sister (II, 7) has a son (III, 7), aged 17, who has had frequent attacks of epistaxis since early childhood. There are no others in the family subject to epistaxis.

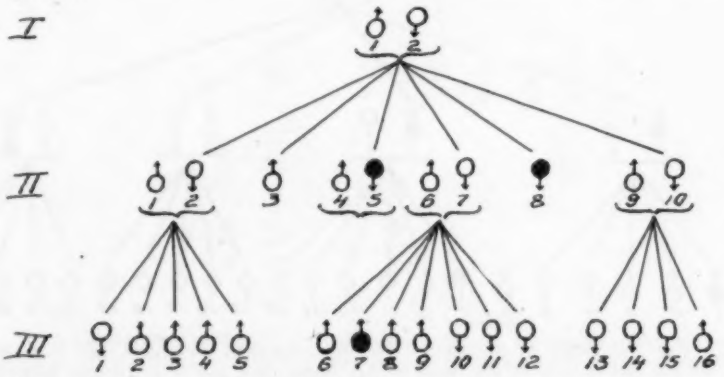

Fig. 4.—Family 27, Steiner 2.

Past History: The patient had measles at 8 years of age. Her menses began at 14, were regular every twenty-eight days, with a duration of six or seven days. The flow was always very profuse.

Present History: When she was about 25 years old, she began to have attacks of moderate epistaxis the day preceding the onset of each menstrual period. Her gums, however, have always bled easily when she cleans her teeth. Twelve years ago she emigrated to this country from Sweden, and two or three years later she began to have red spots on her cheeks. Two years later she noticed them on her hands and wrists. Occasionally she has had slight attacks of dizziness during the past few months. For the past week she has had one to three attacks of severe epistaxis daily, followed by sensations of weakness. The hemorrhages last from ten to fifteen minutes and cease spontaneously.

Physical Examination: The patient was a rather poorly nourished, slenderly built woman. The lips and mucous membranes were quite pale. Over the ears, cheeks, mucous membranes of the lips, tongue and cheeks, wrists,

hands and feet were telangiectases, mostly of the nodular type, pinhead in size, but some were of the spider variety. Some were also seen under the nails of the middle and index fingers and thumb of the left hand. The lungs were negative. The heart was not enlarged, but revealed a presystolic thrill and murmur at the apex, sharply localized. A systolic murmur was also here audible, which could be heard outward to the anterior axillary line and upward to the base, but in both directions with decreasing intensity. The pulmonic second was accentuated.

Blood examination showed red blood corpuscles 2,560,000; white blood corpuscles 5,200; hemoglobin (Dare) 55 per cent.; coagulation time four and a half minutes. Differential count showed polymorphonuclears, 69 per cent.; lymphocytes, 15 per cent.; large mononuclears and transitionals, 24 per cent., and eosinophils, 2 per cent. There were no myeloblasts and but one normoblast seen. There was marked anisocytosis and moderate poikilocytosis.

The patient refused to have the bleeding points in her nose cauterized. Her treatment consisted in the use of rest and iron. After a week's sojourn in the hospital, she left on March 24 to set sail for Sweden from New York on the following day.

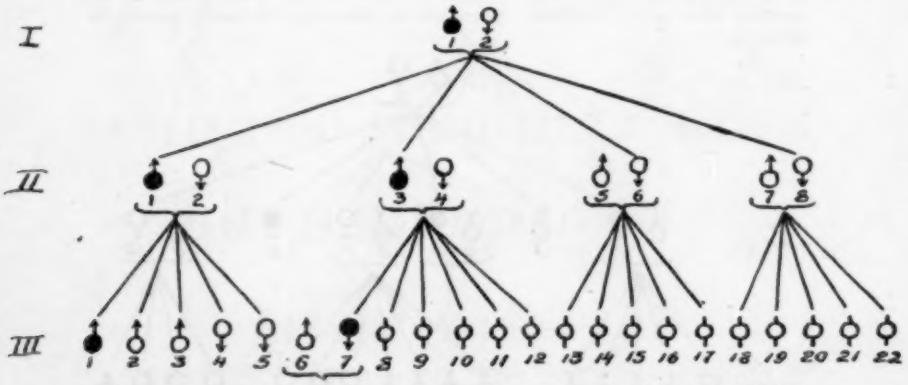

Fig. 5.—Family 28, Steiner 3. The character with the arrow stem both at the top and bottom of the circle in this family tree and in succeeding figures indicates that the sex is not stated.

FAMILY 28 (Fig. 5) (Steiner 3).—There was a history of epistaxis and telangiectases in the family for three generations.

C. L., aged 62 (Hospital No. 86348), was admitted to the Hartford Hospital on my medical service March 15, 1916, complaining of a cough (Fig. 5, II, 3).

Family History: His father (I, 1) who died at 92, had telangiectases and nasal hemorrhages, but further history about him was not obtainable. A brother (II, 1) had a similar condition, as well as his brother's son (III, 1). Of the patient's six children, a daughter (III, 7) suffers from occasional attacks of epistaxis.

Past History: The patient had always enjoyed good health. A few weeks before he entered the hospital, he had a slight operation on his tongue for what he says was a cancer. He had bled from the nose occasionally since boyhood, but recently the attacks had lessened in severity and frequency.

Present History: Four weeks ago he contracted a bronchitis and has coughed considerably ever since. With the cough he expectorates a little clear tenacious sputum. There are no other symptoms.

Physical Examination: The patient was a well-developed, well-nourished Italian. There was evidence of a slight operation on his tongue on the left side. The edges of the healed wound were not ulcerated but felt indurated. The teeth were in very bad condition and the breath was very foul. The lungs revealed medium, moist râles at both bases, posteriorly and in the left axilla. Over his forehead, cheeks and nose pinpoint, nodular and spider angiomas were noted. The largest one of these was located on the left cheek, 4 cm. below a line drawn from the middle of the lower eyelid and 1.5 cm. from the left ala nasi. Under the use of expectorants his cough lessened in frequency, became looser in character and finally left him. A Wassermann reaction was performed on his blood, withdrawn from a vein at his left elbow, with negative results. His teeth were cleaned by Dr. W. N. Butler, one of our dental surgeons, and the patient was discharged from the hospital in good condition on April 12, 1916.

FAMILY 1 (Fig. 6) (Legg, 1876).—There was a history of epistaxis in three generations; developmental telangiectases were noted on the patient's face and trunk, but there was no history of hemophilia.

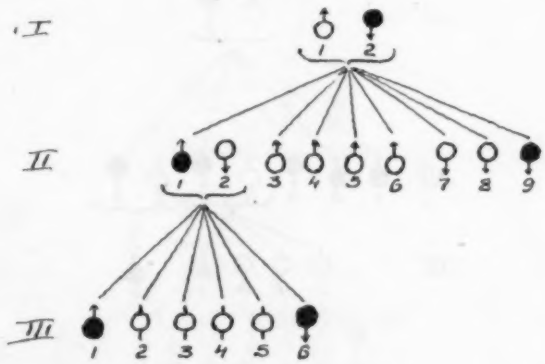

Fig. 6.—Family 1 (Legg).

The patient, II, 1 (Fig. 6), aged 65, gave a history of attacks of epistaxis since boyhood. He has also shown a tendency to bleed profusely from traumatic causes. His mother (I, 2) died from loss of blood and dropsy. One sister (II, 9) is subject to epistaxis. Of his six children a son, aged 27 (III, 1), and a daughter, aged 22 (III, 6), suffer from epistaxis. The patient has numerous small nevi over his face, forehead and various parts of his trunk which first appeared about his 41st year. Violent fits of anger as well as excessive drinking bring on attacks of epistaxis. When seen he had bled every day for six weeks.

FAMILY 2 (Fig. 7) (Chiari, 1887).—There was a history of epistaxis in four generations, with multiple telangiectases on the skin and mucous membranes, a condition diagnosed as hemophilia.

Two sisters (III, 5 and 7) stated that their grandmother (I, 3) and her two brothers (I, 1 and 4) suffered from childhood with frequent and severe attacks of epistaxis, yet lived to ripe old ages. Their mother (II, 2) also had the same difficulty and died at the age of 47 from dropsy, which apparently developed after a long period of nosebleed. Two brothers and one sister (III, 1, 2 and 3) were similarly affected with these severe attacks of epistaxis, but the sister had apparently recovered from these attacks, except at each menstrual period, when the epistaxis was insignificant. The two sisters mentioned above (III, 5 and 7) have bled since childhood from the nose, and one

of them once bled for a long time from the gums. Both of them have telangiectases on their faces and the upper part of their bodies. These are also seen on the mucous membranes of their noses, tongues and lips. III, 5 had four children, the youngest of whom, aged 4, bleeds from the nose. III, 7 had a son, aged 6, who has had epistaxis for four years.

FAMILY 3 (Fig. 8) (Chiari, 1887).—There was history of severe epistaxis in three generations, with multiple telangiectases on the skin and mucous membranes.

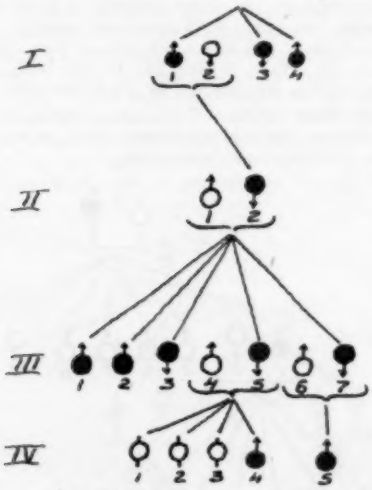

Fig. 7.—Family 2 (Chiari 1).

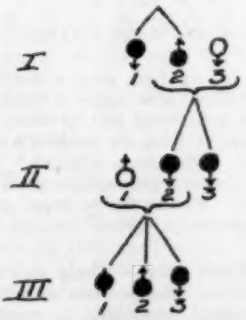

Fig. 8.—Family 3 (Chiari 2). The patient III, 1 died from severe epistaxis.

II, 3 had suffered from childhood with severe attacks of epistaxis. She was about 30 years old when first seen by Chiari and exhibited telangiectases on the skin and mucous membranes of the nose, tongue and lips. She stated that her father (I, 2) and her paternal aunt (I, 1) had had the same trouble. Her sister (II, 2) was likewise affected, as well as her sister's three children (III, 1, 2 and 3). One of them had died some years previously from a severe nosebleed.

FAMILY 4 (Fig. 9) (Rendu, 1896).—There was history of severe epistaxis in two generations; the condition was made a distinct clinical entity by Rendu.

II, 1, aged 52 years, had had severe daily recurring epistaxis for three weeks. His father (I, 1) had died of dysentery, with repeated crises of melena, at the age of 55, and his mother (II, 2) was subject to recurring epistaxis. One brother (II, 2) had also suffered from abundant and recurring epistaxis. Telangiectases were noted on the skin of the face and mucous membranes of the mouth and tongue of the patient. They were also seen, but in less numbers, over the neck and chest.

FAMILY 5 (Fig. 10) (Osler, 1901).—There were attacks of epistaxis from childhood, seven members of the family being subject to it; there were telangiectases on skin of face and mucous membranes of nose and mouth.

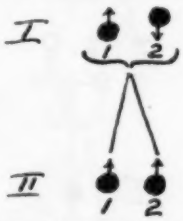

Fig. 9.—Family 4 (Rendu).

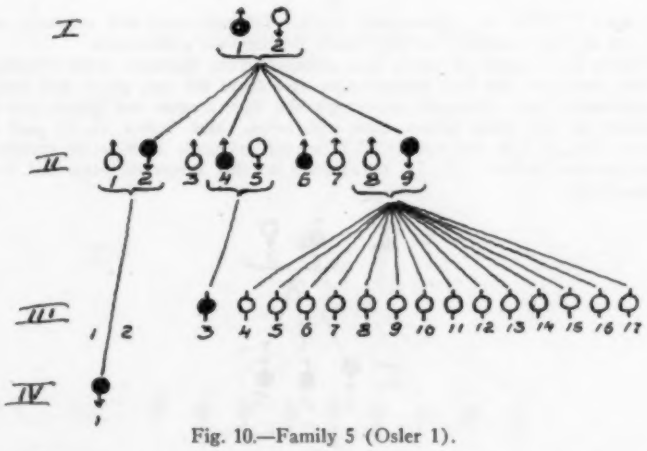

Fig. 10.—Family 5 (Osler 1).

II, 4 began to have attacks of epistaxis in his 10th year. They were not very severe, but recurred almost every day until he was 37 years old, when he was unable to work for nearly three years on account of the weakness and anemia induced by the bleeding. He was 49 years old when first seen by Osler, and exhibited telangiectases on the ears, nose, cheeks, lips and tongue. His father (I, 1) had had attacks of epistaxis, which were never dangerous but very frequent. His oldest sister (II, 2) had bled from childhood from the nose and her granddaughter (IV, 1) had had epistaxis frequently. Another sister (II, 9), also, had bled from the nose and mouth since childhood. His child (III, 3) had likewise occasionally bled from the nose, while a brother

(II, 6) gave a history of epistaxis from childhood with telangiectases of the skin and mucous membranes, which bled at times. This last patient finally died of cancer of the stomach, as revealed by necropsy.

FAMILY 6 (Fig. 11) (Osler, 1901).—Recurring epistaxis had occurred in the members of the family from the 10th year; there were multiple telangiectases of the skin and mucous membranes of the nose and mouth, and telangiectases but no epistaxis in the next generation.

Patient I, 1, aged 49 years, had had epistaxis from his 10th year, varying greatly in severity. From his 18th to his 21st year he was much better, but then the attacks came on again with increased severity. When a boy he first noted the telangiectases, which have increased during the past seven or eight years and are situated on his ears, forehead, cheeks, lips, back, chest, abdomen and hands. One of his sons showed vascular nevi (II, 1).

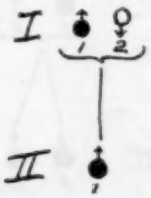

Fig. 11.—Family 6 (Osler 2).

FAMILY 7 (Fig. 12) (Josserand, 1902).—Telangiectases and epistaxis were observed in four members of the family during two generations.

Patient II, 1, aged 56 years, had suffered from epistaxis from childhood. Of late years she had had hemorrhages also from the lips, gums and tongue. Telangiectases were observed on her cheeks, lips, tongue and palate and less markedly on her neck, breast, back and arms. Her father (I, 1) and one brother (II, 2) had suffered from recurrent epistaxis from early childhood, while another brother (II, 3), in addition to this symptom, presented facial telangiectases.

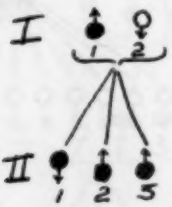

Fig. 12.—Family 7 (Josserand).

FAMILY 8 (Fig. 13) (Brown-Kelly, 1906).—There was severe recurring epistaxis with multiple telangiectases of the skin and mucous membranes in the family for three generations; death of one member occurred from syncope induced by a prolonged epistaxis.

The patient, II, 2, aged 41 years, had suffered from severe recurring epistaxis. Her father (I, 1) had died at 62 years of age from the effects of frequent attacks of epistaxis. A sister (II, 3) has suffered from frequent hemorrhages from her lips, mouth and nose, and has multiple telangiectases on the skin of her face and hands, and the mucous membranes of her nose and mouth. A few have lately developed on the scalp and occasionally give rise to

bleeding when the hair is combed. Her daughter (III, 1) bleeds from her nose and has red spots on her face. The patient (II, 2) finally died from an attack of syncope induced by severe and persistent epistaxis.

FAMILY 9 (Fig. 14) (Hawthorne, 1906).—There was epistaxis in three generations, with telangiectases, a marked family history of these symptoms.

II, 3, aged 49 years, had suffered from childhood with bleeding at the nose, which once required plugging of the nostrils. Her father (I, 1) and her sister (II, 1) had similar attacks and all had telangiectases on their faces.

Fig. 13.—Family 8 (Brown and Kelly).

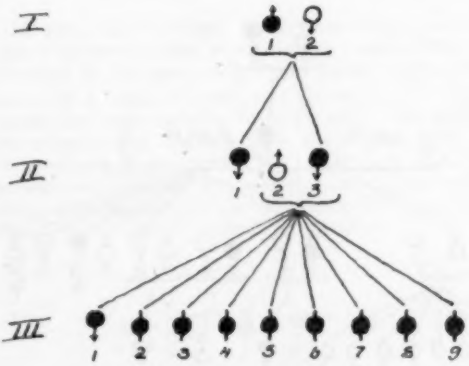

Fig. 14.—Family 9 (Hawthorne).

A few were also seen on the patient's fingers (II, 3) and all of her nine children were subject to recurring nose bleed.

FAMILY 10 (Fig. 15) (Osler, 1907).—Hemorrhages occurred from nose and mouth of one member of the family from the 10th year; there were multiple telangiectases on the skin of his face, ears and lips. A similar condition was observed in three generations.

The patient, III, 1, aged 53 years, is a physician, whose grandfather (I, 1), father (II, 1) and one sister (III, 3) had red spots on their faces. His son

(IV, 1) is subject to attacks of epistaxis which have been frequent but not profuse. III, 1 has bled with great profuseness from his nose and from the telangiectases on his head, face, ears, arm and mucous membranes of his mouth.

FAMILY 11 (Fig. 16) (Parkes-Weber, 1907).—This family gives a history of recurring epistaxis in four generations; telangiectases also were observed in four of the eight members affected with telangiectases.

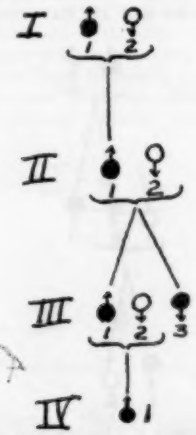

Fig. 15.—Family 10 (Osler 3).

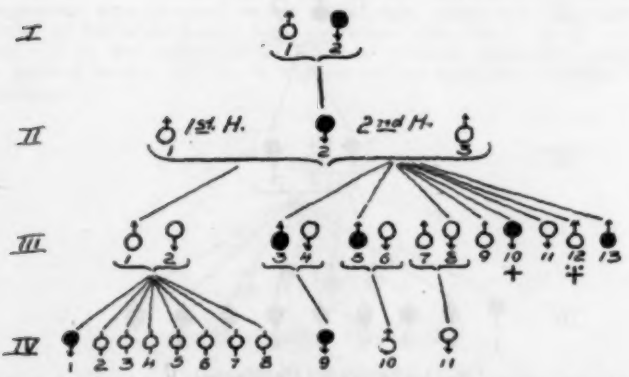

Fig. 16.—Family 11 (Parkes-Weber). The daughter, III, 10 suffered with epistaxis only. The son, III, 12, aged 3 years, died of "brain trouble."

The patient, II, 2, aged 60 years, first noted telangiectases on her face when she was 42 years old. Recurrent attacks of epistaxis had begun a few years earlier. During the last few years they have come on every two or three weeks and are more severe than formerly. The telangiectases are located on her face, ears, lips, tongue, mucous membranes of her mouth and nose and the conjunctival surface of the four eyelids. They are also observed on the

anterior surface of the epiglottis and on the fingers and under the finger nails. All are punctiform save one on the right cheek, which is of the spider nevus type. Her mother (I, 2) was subject to attacks of epistaxis and had one or two spots on her face. By her first marriage, she had a son, whose boy (IV, 1), aged 9, suffers from epistaxis. By her second marriage she has three sons (III, 3, 5 and 13) and one daughter (III, 10) who suffer likewise from epistaxis and two of these sons (III, 3 and 5) have multiple angiomas of the skin and mucous membranes. The oldest son (III, 3) is married and has a boy (IV, 9) who is subject to attacks of epistaxis.

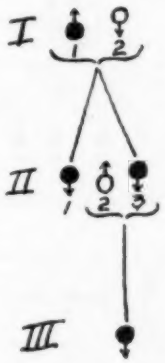

Fig. 17.—Family 12 (Phillips).

FAMILY 12 (Fig. 17) (Phillips, 1908).—Recurring hemorrhages from the nose and mouth occurred in this family in three generations; there were multiple telangiectases of the nose, tongue and buccal mucous membrane.

The patient, II, 3, aged 56 years, was subject to bleeding from childhood from the mouth and more recently from the nose. Her father (I, 1) suffers from violent epistaxis and bleeding from the tongue, while a sister (II, 1) died from hemorrhage of the gums. The patient (II, 3) has a daughter who has telangiectases on her tongue and recently has had attacks of epistaxis. The patient exhibits telangiectases on the mucous membranes of the tongue and nose, as well as on the buccal mucous membranes.

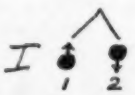

Fig. 18.—Family 13 (Waggett).

FAMILY 13 (Fig. 18) (Waggett, 1908).—There was severe epistaxis in brother and sister; multiple telangiectases of the skin of the face and the mucous membranes of the nose and mouth.

The patient, I, 1, aged 53 years, has had hemorrhage from the nose frequently since his 20th year. He has likewise had hemorrhages from telangiectases on his face and lips. These telangiectases are also seen on the mucous membranes of his tongue and nose. His sister (I, 2) has the same symptoms.

FAMILY 14 (Fig. 19) (Ballantyne, 1908).—This was a family of eight Hollanders who presented telangiectases in five of the six members examined.

The mother (I, 2) of a family of six children exhibited telangiectases on the conjunctiva of the right upper lid, the cheeks, the nose and the lips, but gave no history of hemorrhages from any of them. Her only daughter (II, 2) showed similar spots in almost similar locations, but has one also under the nail of the fourth finger of her right hand. She has bled from the nose rather frequently. A brother, II, 3, had no spots, but was subject to attacks of epi-

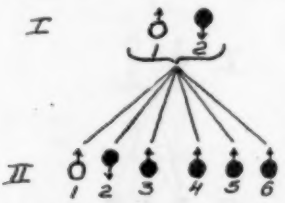

Fig. 19.—Family 14 (Ballantyne).

staxis. Another brother, II, 4, had a few telangiectases on the tip of his nose, inner surface of his lower lip and the tip of his tongue. The brothers, II, 5 and 6 showed small elevated red spots about the tip of the tongue as II, 4 did.

FAMILY 15 (Fig. 20) (Gottheil, 1908).—There were telangiectases in two generations; epistaxis in three.

The patient, II, 5, aged 40 years, has bled periodically and spontaneously from his nose, tongue and lips as long as he can remember. The hemorrhages

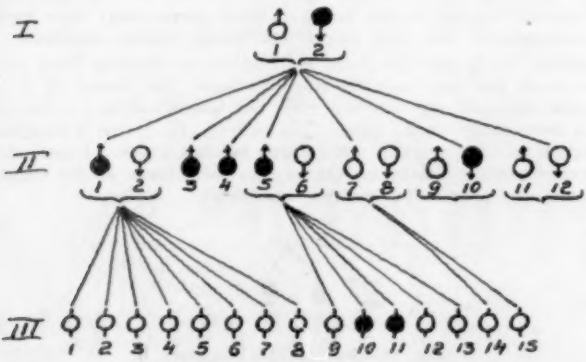

Fig. 20.—Family 15 (Gottheil).

vary in frequency from several in one day to one a week, but recently they have come on more often. His mother (I, 2) had spots on her lips and was said to have died from hemorrhages twenty-seven years ago. His brothers (II, 1, 3 and 4) have also had hemorrhages from the nose, as has also one sister (II, 10). None of them have had telangiectases. Two of his children (III, 10 and 11) have bled from the nose also.

FAMILY 16 (Fig. 21) (Hanes, 1908).—There were recurring hemorrhages in four generations of one family, and multiple telangiectases of skin and mucous membranes, but no symptoms of hemophilia.

The patient, II, 4, aged 53 years, had been subject to epistaxis from childhood. Generally her nose bleeds once or twice a week and sometimes every day. Since her 37th year the epistaxis has increased in severity, as well as the telangiectatic spots on her face, lips and tongue. Some are also seen on the ears, the hard palate and the gums of the lower jaw, as well as on the nasal mucous membranes. On the pads of the fingers and under the nails many small purple spots are visible. The conjunctiva of the right lower lid exhibits one of bright red hue. Her mother (I, 2), who died at 48 from heart disease with dropsy and cough, had suffered all her life with severe epistaxis. Her brothers (II, 1 and 2) were also troubled all their lives with a similar severe epistaxis and both showed red spots on their face and lips. One son (III, 1) has been greatly troubled from severe hemorrhages from telangiectases, which

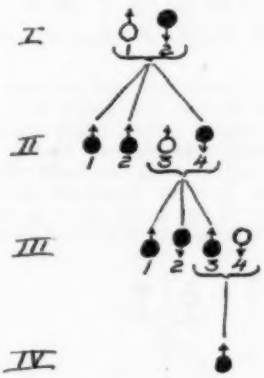

Fig. 21.—Family 16 (Hanes 1).

are numerous on his lips and tongue. Frequently he injures one of these labial or lingual telangiectases while eating, so that blood will spurt from the injured spot and render further progress with the meal impossible. Profuse hemorrhages from two telangiectases under the nail of the left middle finger have interfered greatly with his occupation as a fireman. Occasionally he has attacks of epistaxis. In every instance the hemorrhages result from slight traumatism. The other son (III, 3) had spots on his lips and face and had bled easily from his nose all his life. Her grandson (IV, 1), a son of III, 3, has two small red telangiectases at the mucocutaneous junction, but has never bled from the nose. Her daughter (III, 2), on the other hand, has frequently bled from the nose most profusely and presents on her face small pinpoint telangiectases. Several of a violaceous hue are seen on the lower lip and one bright red in color is noted on the dorsum of the tongue. The mucous membranes of the nose and the pads of the fingers and under the nails are other locations where these spots are found.

FAMILY 17 (Fig. 22) (Hanes, 1908).—There was epistaxis in four sisters and multiple telangiectases affecting chiefly the mucous membranes, but no symptoms of hemophilia.

The patient, II, 4, aged 46 years, had suffered extremely throughout childhood and youth from severe epistaxis, which frequently necessitated plugging of the nostrils. She also presented telangiectases under the eyes, at the bases of the alae nasi, on the conjunctivae, both lips, tip of the tongue, hard and soft palate, and nasal mucous membrane. She later developed an endocarditis. Her father (I, 1) had suffered from youth with recurring epistaxis, which came on daily during the later years of his life. One sister (II, 7), who

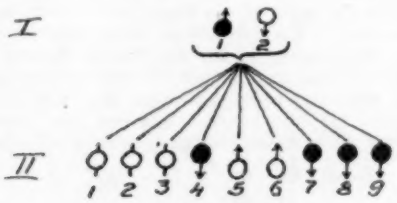

Fig. 22.—Family 17 (Hanes 2).

died at the age of 27, during childbirth, had bled profusely and frequently from the nose. Another sister (II, 8) had bled almost daily as far back as she could remember. She also presented definite telangiectases on her left cheek, lips, tip of tongue and nasal mucous membrane. Another sister (II, 9) bleeds two or three times weekly from the nose, but never very severely. She has a few telangiectases on the lips, tip of the tongue and nasal mucous membrane. Her two brothers (II, 5 and 6) are practically free from the disease, but bleed readily from the nose during a cold or after traumatism.

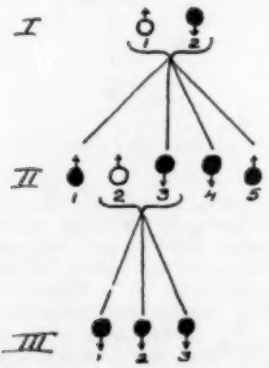

Fig. 23.—Family 18 (Laffont).

Family 18 (Fig. 23) (Laffont, 1909).—A marked family history of telangiectasis, with a history of epistaxis in three out of the eight affected in the three generations.

The patient, II, 3, aged 48 years, noted eight years previously that telangiectases were appearing on the periphery of the scalp, the ear, the face, the breast and the back. Some had disappeared spontaneously. She had been subject since puberty to repeated attacks of epistaxis. Her mother (I, 2) had had, toward her 62d year, small telangiectases appear on her ear, neck, chest and

arm. There was no history of epistaxis in this instance. Her sister (II, 4) had similar spots on her ears, nape of neck and arm, but no epistaxis. Her elder brother (II, 1) had no telangiectases, but had spat up blood for about a year from varicosities of the pharynx, while her younger brother (II, 5) had some spots on his chest and back, but no hemorrhages. Her eldest daughter (III, 1) showed some telangiectases on her face and body, and had been subject to repeated epistaxis. Another daughter (III, 2) showed spots on the dorsal aspect of the forearm, the neck and trunk, while the third daughter (III, 3) presented spots on her face, neck, breast and back.

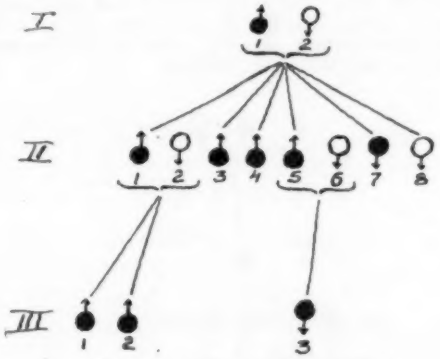

Fig. 24.—Family 19 (Langmead).

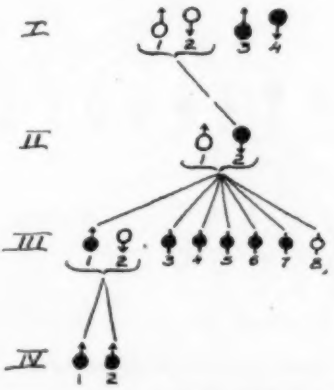

Fig. 25.—Family 20 (Audry).

FAMILY 19 (Fig. 24) (Langmead. 1909).—Telangiectases were noted in eight members of a family for three generations, epistaxis being observed in eleven instances.

The patient, II, 1, aged 68 years, was subject for about twenty years to frequent epistaxis. Occasionally telangiectases on his face and tongue have burst out bleeding. The telangiectases are seen on his face, lower lip, tip of tongue, palate and a few on the neck, chest and back. His father (I, 1) was

affected with epistaxis and telangiectasis, but his mother (I, 2) had epistaxis only. His three brothers (II, 3, 4 and 5) were subjects of epistaxis and telangiectasis, as was also one sister (II, 7). One son (III, 1) has nevoid patches and epistaxis, while the other (III, 2) has epistaxis only. A niece (III, 3) has similar patches and recurring epistaxis.

FAMILY 20 (Fig. 25) (Audry, 1911).—Epistaxis and telangiectases were noted in four generations.

The patient, III, 1, aged 70 years, had had attacks of epistaxis for many years, but lately they had increased greatly in frequency. Numerous telangiectases were seen on his face, lips, tongue and palate, and more sparsely on his trunk and upper extremity. His mother (II, 2) had epistaxis and telangiectases, as had also a great uncle and a great aunt. Five of the patient's brothers and sisters were similarly affected, as well as his two sons. Several nephews and nieces also had the same condition.

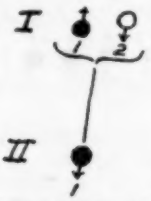

Fig. 26.—Family 21 (Osler 4).

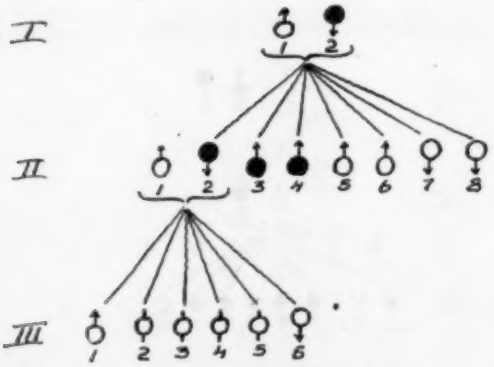

Fig. 27.—Family 22 (Van Wagenen).

FAMILY 21 (Fig. 26) (Osler, 1911).—Telangiectases were observed in two members of a family for two generations.

The patient, II, 1, aged 35 years, had suffered from childhood from recurring epistaxis. She also had shown later some telangiectases, but they had increased considerably during the last six years. They were situated on the nasal mucous membranes, the tongue and the lips. One was also seen under the nail of the left index finger. Her father (I, 1) had suffered for many years from severe recurring epistaxis and his face was covered with telangiectases.

FAMILY 22 (Fig. 27) (Van Wagenen, 1912).—Epistaxis and telangiectases were observed in four members of a family during three generations.

The patient, II, 2, aged 32 years, has had bleeding from the tongue and nose during the past nine years. Telangiectases were seen on the nasal mucous membranes, tongue, face and arms. Her mother (I, 2) has had frequent attacks of epistaxis since early childhood and two of her brothers (II, 3 and 4) have had a similar history.

FAMILY 23 (Fig. 28) (Sequeira, 1913).—Epistaxis and telangiectases were observed twice in two generations.

The patient, I, 2, aged 55 years, has noted red spots appearing on her face and fingers during the past five or six years. Occasionally she has had

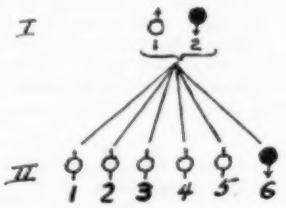

Fig. 28.—Family 23 (Sequeira).

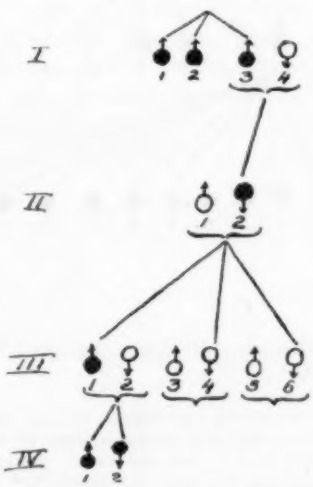

Fig. 29.—Family 24 (Gjessing).

hemorrhages from these spots. Telangiectases were also found on the tongue, mucous membrane of the lower lip, hard palate, uvula and the lower internal surface of the left labium majus. She had had also slight bleeding from the nose. One daughter (II, 6) gave a history of occasional attacks of epistaxis.

FAMILY 24 (Fig. 29) (Gjessing, 1915).—Epistaxis and telangiectases were observed for four generations, one member being affected also with endocarditis and hemorrhagic retinitis.

The patient, III, 1, 51 years of age, has had severe epistaxis from childhood, which lately has increased in frequency and violence. In his late twen-

ties telangiectases began to develop on his face and the mucous membranes of his mouth. They are now also seen on the ears, under the chin and on the neck, as well as on the nose, the tip and base of the tongue, the hard palate and the lower right eyelid. On the left arm two small ones are also noted, others under two finger nails and still others on the dorsal and volar aspects of the fingers. Besides the hemorrhages coming from the nose, bleeding has been observed from spots on his cheeks, tongue and eyelid. His maternal grandfather (I, 3) and the latter's two brothers (I, 1 and 2) had suffered from severe epistaxis, but it was not known whether they had facial angiomas. His two children (IV, 1 and 2) have suffered since childhood from severe epistaxis. The son (IV, 1) has telangiectases on his face, nasal mucous membranes, tongue, and hard palate. He is affected with a disease of the heart and has hemorrhagic retinitis. He has become so anemic from the hemorrhages that his hemoglobin has fallen to 25 (Tallqvist). The daughter (IV, 2) has a few small angiomas on her cheeks, which have appeared during the last two years.

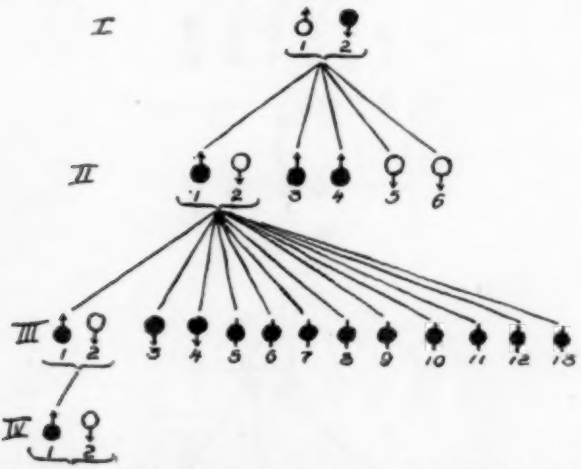

Fig. 30.—Family 25 (Hutchison and Oliver). Patients III, 5 to 13, inclusive, suffered with epistaxis only.

FAMILY 25 (Fig. 30) (Hutchison and Oliver, 1916).—There was a history of epistaxis in four generations, with telangiectases observed in three generations.

The patient, III, 1, aged 48, had had attacks of epistaxis for as long as he could remember, but during the last two years they had become more severe, especially in the morning. Telangiectases appeared first eight years ago and gradually increased in number. They were situated on the ears, cheeks, nose, lips, buccal mucous membranes, hard palate, tip and under surface of the tongue, the posterior pharyngeal wall, the soft palate, the uvula and the right hand. Spontaneous bleeding had occurred from those on the lips, and this was sometimes preceded by a feeling of soreness. He had also bled occasionally from the ears, about the fossa of the helix and from the corner of the right eye, as well as from the gums and the inside of the mouth. From the last situation the hemorrhages appeared especially after very hot drinks. About a year ago he bled from the rectum, on straining. His Wassermann reaction was negative. His father (II, 1) had had frequent spontaneous attacks of epistaxis from childhood and for the last six years has bled occasionally and

spontaneously from the spots on his nose. During the last five or six months he has bled somewhat from his gums. Two or three years ago he also had occasional bleeding from the rectum. For many years he has had telangiectases on his face. They were also noted on his ears, cheeks, sides of nose, lips, dorsum of tongue, hard palate and buccal mucous membranes, back and shoulders. His son (IV, 1) has had attacks of epistaxis as long as he could remember, but during the last two years they have become more infrequent. Some telangiectases were noted on his right cheek, the tip of his tongue, the mucous membranes of his lips and on his right shoulder. There was a definite history of nose bleeding in other members of the family (I, 2, II, 3 and 4, III, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13).

CONCLUSIONS

From a consideration of the histories of these three families affected with hemorrhagic telangiectasis and those previously recorded we may conclude that heredity is the only important etiologic factor as yet discovered and that both sexes are equally affected and equally capable of transmitting the disease. Microscopically a developmental defect has been found in the dilated capillaries, as the elastic and muscle fibers appear to be wanting. The capillaries, consequently, are very liable to produce hemorrhages by their rupture, which is induced either spontaneously or by traumatism. The hemorrhages from the nose are generally seen early in life, while the telangiectases are a later development. The cautery in most instances offers the best results in the treatment of the bleeding telangiectases.

A CLINICAL STUDY OF THE SECRETIONS ON THE PROXIMAL AND DISTAL SIDES OF THE PYLORUS *

A. S. ROBINSON, M.D.
CLEVELAND

The secretions on the proximal and distal sides of the pylorus have been studied in 125 patients entering Lakeside Hospital during the past year, complaining of various gastro-intestinal disturbances. The secretions were obtained on a fasting stomach in all cases and in many of the cases the secretory and motor function of the stomach was also determined.

The Einhorn and Rehfuss tubes were used. The Rehfuss tip, being oval, with slits on the side, and relatively large, when passing through the pylorus, became plugged by the walls of the pylorus and no secretion could be aspirated during this time. To remedy this a small opening was made in the end.

The tube was passed, as a rule, on a fifteen-hour fasting stomach. The tip was introduced into the mouth when the patient was lying down. The patient then swallowed and as soon as the tip passed into the esophagus he assumed the sitting posture, being requested not to swallow any more and to expectorate all saliva. By supporting the tube and having the patient breathe slowly and deeply, the tip slowly passes down the esophagus into the stomach. The tubes are marked at 35 cm., 50 cm., 60 cm., 70 cm., etc., from the tip. When the 35 cm. mark passes the teeth, the tip is at the cardiac orifice. The patients were then placed on their right side. The tip then, together with what secretions are present, gravitates toward the pylorus. No secretions can be aspirated until both the tip and the gastric secretions reach the pylorus. The distance from the pylorus to the mouth is indicated by the second mark (50 cm.) on the tube. Specimens were then obtained every ten minutes until the tip passed through the pylorus into the duodenum. This took, in normal cases, about thirty minutes.

Three methods were used in obtaining the specimens:

First, the secretion was aspirated with a 20 c.c. glass syringe connected directly to the tube. It was difficult not to apply too much suction, which drew the mucosa into the openings of the tip, ruptured capillaries and almost invariably gave a positive guaiac test.

Second, in most cases sufficient secretion could be obtained by

* Submitted for publication July 29, 1916.
* From the Medical Clinic of Lakeside Hospital, Cleveland.

siphoning or by the gravity method. The secretions came at irregular intervals. Here the chance of accidental hemorrhage is ruled out. The amount of secretion present at any given time in the stomach and the time it left the stomach cannot be accurately determined.

Third, in this method the tube was connected to a Wolff bottle. Small test tubes were hung by a thread in the bottle under the cork. Then a vacuum was made in the bottle by a Potain pump, and the contents of the stomach or duodenum were aspirated. When the test tube became full it was replaced by another, or the secretions were collected in the bottle. In this method uniform suction is obtained, all the secretion may be aspirated and measured at any given time and individual specimens at varying periods may be obtained with ease.

In obtaining the secretions with the duodenal tube the following sources of error must be considered: The stimulation of the tube in the mouth, together with some nausea, stimulates the flow of saliva, which, if swallowed, being alkaline, will decrease and often completely neutralize the free hydrochloric acid. Then, too, strong suction draws the mucosa against the openings and bursts capillaries, which will give a positive guaiac test and often microscopic blood is seen.

The average gastric secretion of the fasting stomach was found to be a clear, opalescent fluid. About 10 c.c. could be aspirated every ten minutes. A small amount of mucus was invariably present. In the same individual the acidity of the fasting stomach was found to be about one half that of the acidity after an Ewald test meal. Microscopic examination showed small shreds of mucus. A few white blood cells, usually clumped in mucus, were found, and some degenerated, squamous epithelium and bacteria of varying types.

The normal duodenal secretion is of a clear amber color. About 15 c.c. can usually be aspirated and then about 10 c.c. every ten minutes. There is no free hydrochloric acid present, the total acidity being about 5 per cent. lower than that of the gastric secretions. It remains of an amber color for several days, gradually changing to green as the bilirubin becomes oxidized to biliverdin. Microscopic examination shows fewer white blood cells, epithelium and bacteria. A large diplococcus was the commonest type seen.

When free hydrochloric acid is present, the bile pigments are precipitated. Instead of a clear, amber fluid, it is of a cloudy yellow, and a sediment settles on standing. It becomes green very rapidly, depending on the amount of free hydrochloric acid. Microscopically a fine yellow sediment is seen, which resembles amorphous urates. On neutralizing the free hydrochloric acid with sodium hydroxid the fluid becomes of a clear amber color.

The secretory function was determined in most cases by giving the patients an Ewald test meal. The Rehfuss tube was then passed and

specimens obtained every fifteen minutes until the stomach was empty. In this way the acidity was determined during the whole process of digestion, and not at just one point; and the time required to empty the stomach was also determined. The specimens obtained were examined for free hydrochloric acid, total acidity, lactic acid, blood and bile. The amount of mucus was noted. A microscopic examination was made for red blood cells, white blood cells, epithelium, bacteria and gallstone detritus. In cases of achylia or subacidity the Wolff-Junghan's test was made. The gastric motor function was determined by passing a stomach tube three hours after a house meal, and by the Roentgen ray.

The secretions on the proximal and distal sides of the pylorus were studied in the cases shown in Table 1. From the number and variety of cases only the following conditions will be considered: gastric neurosis, gastric ulcer, gastric carcinoma, duodenal ulcer, obstructive jaundice, cholelithiasis, cholecystitis and pernicious anemia.

TABLE 1.—Diseases in Which Pyloric Contents Were Studied

Disease	No. Cases	Disease	No. Cases
Pernicious anemia	6	Cholelithiasis	10
Gastric ulcer	18	Cholecystitis	3
Duodenal ulcer	5	Gastric purpura	1
Gastric carcinoma	12	Cerebrospinal syphilis	3
Gastric neurosis	36	Nephritis	3
Neurasthenia	5	Vomiting of pregnancy	2
Chronic gastritis	5	Tuberculosis	2
Chronic constipation	10	Epigastric hernia	1
Obstructive jaundice	3		

GASTRIC NEUROSIS

Rehfuss[1] and others have shown that a very high acidity may be present in apparently healthy persons and cause no discomfort. That some have pain and discomfort with a degree of acidity that in others causes no distress we in our ignorance attribute to a neurosis, in which the threshold of excitability is low.

In 40 per cent. of the patients entering Lakeside Hospital during the past year, complaining of various gastro-intestinal symptoms, nothing pathologic could be found in the gastric secretions to account for the distress except an increase in acidity above that considered as the average. These cases were diagnosed gastric neurosis and fell into

1. Rehfuss, Bergein and Hawk: Jour. Am. Med. Assn., 1914, **63**, 909.

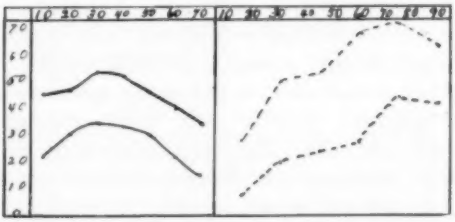

Fig. 1.—Acidity curves for cases of gastric neurosis. The solid lines indicate the average acidity of the secretions of the fasting stomach in forty cases. The dash line indicates the acidity of the secretions following an Ewald meal. The upper curves in each instance indicate the total acidity; the lower, the free hydrochloric acid.

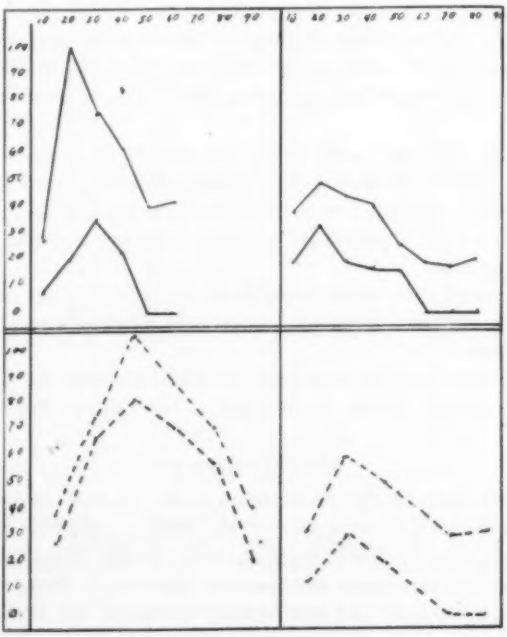

Fig. 2.—Acidity curves in four cases of gastric neurosis with chronic constipation, the upper two (Cases 77 and 98) being of the secretions of the fasting stomach, the lower two (Cases 34 and 58) of the secretions of the stomach after an Ewald meal. The upper curve in each of the four cases indicates the total acidity; the lower, the free hydrochloric acid.

three general classes: (1) gastric neurosis secondary to infection, as tuberculosis, influenza, syphilis and pelvic inflammatory conditions; (2) gastric neurosis associated with chronic constipation; (3) gastric neurosis secondary to some mental or physical strain.

The symptoms complained of were many and varied. The commonest were epigastric distress after meals, flatulence, anorexia, heartburn, nausea and pain. The pain varied in the same individual in time, location, intensity and duration. There was invariably an absence of tenderness and muscle rigidity. In the cases in which the secretions were examined more than once, they showed a marked variation in the acidity. The average acidity curve made from forty cases of the secretions of the fasting stomach, given in Figure 1, shows a constant relation of the free hydrochloric acid to the total acidity, a slight rise in acidity for the first half hour and then a gradual fall. The duodenum was entered on an average in forty minutes. The individual curves varied greatly, no two being alike. Figure 2 shows curves in four cases of gastric neurosis associated with chronic constipation, two on a fasting stomach and two after an Ewald meal. These show the futility of comparing the acidity curves in different individuals.

To summarize the results of the investigations in cases of gastric neurosis, I would say that in 40 per cent. of cases examined nothing pathologic could be found to account for distress.

A diagnosis of a pathologic condition cannot be made from subjective symptoms.

Gastric neurosis is most commonly secondary to an infection, as tuberculosis, syphilis, influenza, chronic constipation and mental or physical strain.

The secretions on the proximal and distal sides of the pylorus and the gastric acidity curves show nothing constant or typical of this condition.

GASTRIC CARCINOMA

The secretions on the proximal side of the pylorus were examined in eleven cases of carcinoma of the stomach, liver or colon. The secretions on the distal side were obtained in only three cases (probably because the carcinoma involved the pylorus). Two patients had carcinoma of the liver and one had carcinoma of the hepatic flexure of the colon.

In all the cases of gastric carcinoma there was no free hydrochloric acid, with one exception. In two cases of carcinoma of the liver and stomach free hydrochloric acid was present. One of these cases was found at necropsy to be complicated with a duodenal ulcer. Lactic acid was present in only three of the cases. There was an increased

bacterial flora in all specimens examined. The Wolff-Junghan's test was done in only the last three cases. It was positive in two cases of gastric carcinoma, and only faintly positive in a case of carcinoma of the splenic flexure of the colon.

The case of carcinoma of the pylorus had a very atypical clinical course. The patient was a Jew, aged 45. He entered the hospital April 9, 1915, complaining of pain between meals, eructation of gas and a bitter fluid. House meal, removed in three hours, showed 200 c.c. of a greenish, sour-smelling liquid, with free hydrochloric acid 40, total acidity 100. The benzidin test

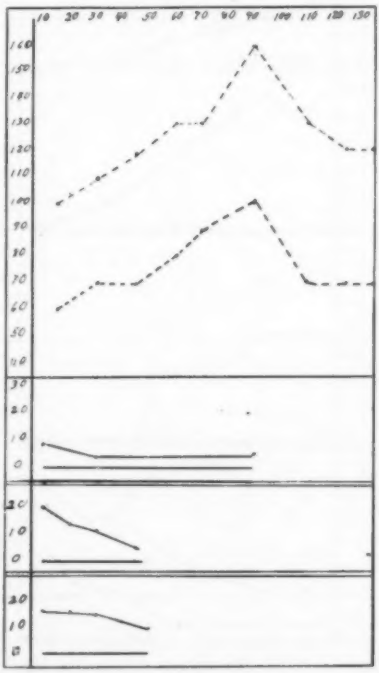

Fig. 3.—Acidity curves in cases of carcinoma of the stomach (Cases 120, 49, 83 and 68). In Case 120 each of the two dash lines indicates the acidity of the secretions following an Ewald meal. The solid lines in the other three cases indicate the acidity of the secretions of the fasting stomach. The upper curve of the four cases indicates the total acidity; the lower the free hydrochloric acid.

was positive. A carbohydrate test meal (Ewald) was given, and 30 c.c. were removed in one hour. There was free hydrochloric acid 30, with total acidity 50. No treatment was given the patient here. He had no discomfort until Oct. 1, 1915, when he began again to have pain after eating, and he became constipated. Oct. 17, 1915, he had a sharp pain in the epigastrium, followed by a sensation of weakness. He came to the hospital Oct. 18, 1915. The right side of his epigastrium was tender and rigid. A house meal was given and

200 c.c. were removed in three hours, showing free hydrochloric acid 74, total acidity 124. A carbohydrate meal was given and 75 c.c. were removed in one hour, showing free hydrochloric acid 64, total acidity 86, lactic acid negative, and guaiac test negative. An Einhorn duodenal tube was passed on a fifteen-hour fasting stomach; 150 c.c. of a coffee ground fluid were removed. The guaiac test was positive. The spectroscope showed the bands of oxyhemoglobin. Microscopic examination showed starch cells, red blood corpuscles and desquamated epithelium. The first specimen showed free hydrochloric acid 34, total acidity 50; the second, taken in forty-five minutes, showed free

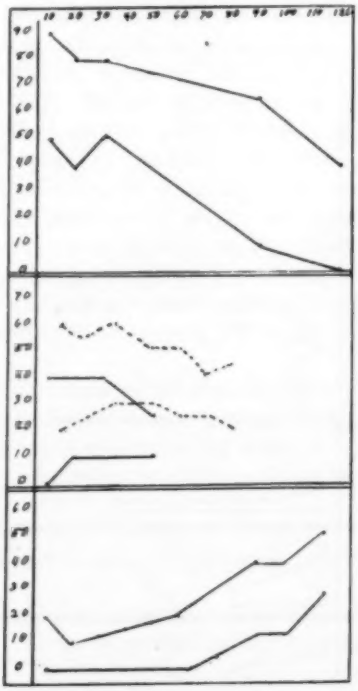

Fig. 4.—The upper part of the figure represents the acidity curves of a case of carcinoma of the liver (Case 46); the middle, of a case of carcinoma of the liver and stomach, with duodenal ulcer (Case 60); and the lower, of a case of carcinoma of the colon (Case 53). The solid lines in each case represent the acidity of the secretions of the fasting stomach; the dash lines the acidity of the secretions following an Ewald meal. The upper curve in each case represents total acidity; the lower, free hydrochloric acid.

hydrochloric acid 66, total acidity 110; and the third, taken in sixty minutes, showed free hydrochloric acid 70, and total acidity 128. The duodenum was not entered.

A diagnosis was made of ulcus ventriculis. The patient was given the Sippy routine. He gained in weight, got immediate relief from the pain and eructations, and when discharged, Nov. 13, 1915, he was eating a liberal diet with no discomfort. He had no further discomfort until the middle of

March, 1916. He then began to belch gas and experience heartburn. There was no pain, tenderness or vomiting. This became progressively worse, so he came to the hospital again March 29, 1916. Examination showed the stomach to be dilated. There was visible peristalsis, and a firm, movable mass was palpable to the right of the umbilicus. A duodenal tube was passed on a twenty-hour fasting stomach. Food particles were present. The duodenum was not entered. The acidity curve is plotted in Figure 3 (Case 120). The Roentgen ray showed obstruction at the pylorus, ptosis of the stomach and very little peristalsis. The patient was again put on the Sippy treatment, to see whether the retention was due to an organic obstruction or to irritation of the mucosa at the pylorus. In two weeks the Roentgen ray showed as much retention. Six hundred c.c. were removed three hours after a house meal, with free hydrochloric acid 60, total acidity 100. He was transferred

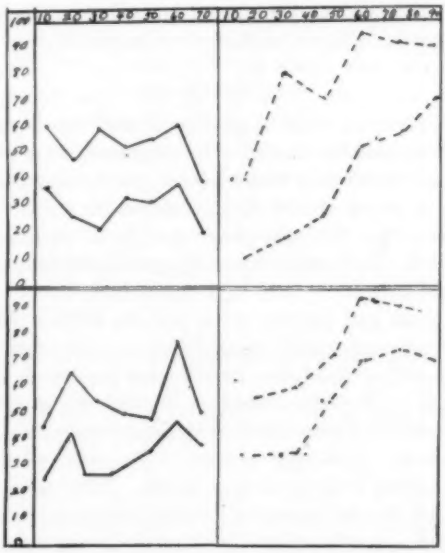

Fig. 5.—Average acidity in sixteen cases of gastric ulcer, the solid lines indicating the acidity of the secretions of the fasting stomach; the dash lines, the acidity after an Ewald meal. The upper curve in each case indicates total acidity; the lower, the free hydrochloric acid.

to the surgical service. Operation revealed a hard mass at the pylorus, and the surrounding lymph glands were hard; section of one showed a carcinoma simplex. The interesting features here are the typical signs and symptoms of a gastric ulcer, followed by retention, the presence of carcinoma four months later with a metastasis into the lymph glands and hyperacidity. A posterior gastro-enterostomy was done. The mass at the pylorus will be removed at a later date by Dr. Crile, so sections of the mass have not been seen.

The question arises: Did the patient have a gastric ulcer and the carcinoma develop in the past four months, or were the symptoms all due to carcinoma? This cannot be answered.

The acidity curve was plotted in eight of the cases in which sufficient specimens were obtained. In four cases of gastric carcinoma the curves show no free hydrochloric acid. The total acidity either remains constant or diminishes. In the one case above described the curve shows a sharp rise.

In carcinoma of the liver free hydrochloric acid was present (Fig. 4). In both cases the acidity curve descends. In the case of carcinoma at the hepatic flexure of the colon, there was a primary fall and then a late rise (Fig. 4). The same type of curve was obtained in cases of pernicious anemia, with the exception that there was no decrease in the total acidity, which remained practically constant.

In general, then, we can say that in achlorhydria, simple and malignant, the acidity curve has a tendency to descend.

GASTRIC ULCER

There were eighteen cases of gastric ulcer in this series, in which a positive diagnosis could be made. The diagnoses were made from the history of hematemesis and blood in the gastric secretions, or by the Roentgen ray in cases of old chronic ulcers or scars. In these few cases it was seen that the pain varied greatly in location and time of occurrence. It is of no more value diagnostically than that found in gastric neurosis.

The tenderness and rigidity were present in over 90 per cent. of cases, whereas pressure usually gave relief in cases of gastric neurosis. The nausea, vomiting and hematemesis were present in most cases.

The duodenal tube passed through the pylorus in only two cases. One case had an old callous ulcer on the lesser curvature, as shown by the Roentgen ray. This was excised. The tube went through the pylorus in the other case in twelve hours. This patient was subsequently operated on, on account of severe hemorrhage, and a pyloric ulcer was found.

This patient was a woman, aged 28. In August, 1914, she began to have pain across her back. In May, 1915, she began to belch gas, which relieved the heavy feeling in her stomach. Later the gas was accompanied by bitter acid eructations, which kept increasing in amount. Sept. 18, 1915, she began to experience sensations in her abdomen resembling fetal movements. Sept. 20, 1915, she started to vomit, at intervals from three to four days, generally four hours after eating. On one occasion she noticed food present in the vomitus which she had eaten twenty-four hours previously. She lost 20 pounds in three months. She entered the hospital Dec. 8, 1915.

Physical examination showed the stomach was distended. There was visible peristalsis and a succussion. There was muscular rigidity and tenderness in the epigastrium. Just below the costal margin in the right nipple line a firm mass, about the size of a walnut, was palpable. A stomach tube was passed and 48 ounces of fluid were removed. This showed free hydrochloric acid 20, total acidity 48. The guaiac test was negative. Cranberry seeds were present which she had eaten forty-eight hours before. From the marked obstruction,

with practically no pain preceding it, and a history of syphilis in the husband, the possibility of the obstruction being due to a gumma was considered, although the Wassermann reaction on the blood was negative. She was given anti-syphilitic treatment and put on a soft diet. She gained 18 pounds in twenty-two days. The peristalsis became less, the stomach showed less retention, and the patient was more comfortable. On Jan. 9, 1916, she vomited, felt very weak and had several black, tarry stools. The hemorrhage continued until Jan. 11, 1916. Her hemoglobin was then 40.1, red blood cells 1,424,500. She was transfused with blood, and a laparotomy was done. A large ulcer was found at the pylorus. Sutures were passed through the mass to stop bleeding and a posterior gastro-enterostomy done. The patient recovered.

In one other case there was a severe hemorrhage. The hemoglobin was 40, red blood cells 800,000. She was transfused and then given the Sippy diet without alkalies, there being a hypoacidity. This patient is gaining in weight and has no gastric distress. Operation will not be recommended. The Wolff-Junghan test is negative.

Three of the patients with gastric ulcer came in for diagnosis. No treatment was given them here.

The other cases, twelve in number, were given modifications of the Sippy routine. In most cases there was relief from nausea, vomiting and pain on the second day. About the second week their appetite returned. The majority gained in weight. In comparison with the Lenhardtz routine, the patients on the Sippy routine got relief quicker, and gained more in weight and strength. The routine followed is given in Table 2.

TABLE 2.—DIET IN THE MODIFIED SIPPY TREATMENT*

Days	Milk and Cream, Ounces of Each, 6 a.m. to 8 p.m.	Soft Eggs		Cereal and Sugar, Ounces	Cream Soups, Ounces	Jellies, Ounces	Stewed Fruit, Ounces	Toast
		A. M.	P. M.					
1	½ per hr.							
2	1 per hr.							
3	1½ per hr.							
4	1½ per hr.	1	1					
5	1½ per hr.	2	2					
6	1½ per hr.	2	2	3 noon				
7	1½ per hr.	2	2	3 twice a day				
7 to 14	1½ every 2 hr.	2	2	3 twice a day	3			
14 to 21	1½ every 2 hr.	2	2	3 twice a day	3	3	2	
21 to 28	1½ every 2 hr.	2	2	3 twice a day	3	3	3	Twice a day

Before discharging the patients, they were given a liberal diet, with no alkalies. A test meal was then obtained. If they had a return of their gastric symptoms, or if the gastric analysis showed a hyperacidity, they were advised to continue taking alkalies and a suitable diet was suggested.

As a modified B. W. Sippy treatment for gastric ulcer I would give the following:

1. Absolute rest in bed for three weeks, with 1 dram of bismuth subcarbonate in 3 ounces of water each morning before feedings are begun.

Midway between the feedings the two following are given alternately:

2. Ten grains each of heavy calcined magnesia and sodium bicarbonate in ½ ounce of water.

3. Ten grains each of bismuth subcarbonate and sodium bicarbonate in ½ ounce of water.

As a diet the course outlined in Table 2 is given.

THE RELATION OF THE ACIDITY CURVES IN THE FASTING STOMACH AND AFTER AN EWALD MEAL

The acidity curve in patients having the same pathologic conditions, such as in gastric ulcer, were compared. The comparisons showed a marked individual variation in both the fasting secretions and in those obtained after an Ewald meal.

In comparing the curves having different pathologic conditions no uniformity was found. No curve was demonstrated as typical of a gastric ulcer or of a duodenal ulcer.

By grouping all the cases and plotting a curve from the average acidity, a curve was obtained which represented the average conditions. Such a curve can only be plotted accurately with a large number of cases; for the individual variations are so great. The curves shown in Figure 5 cannot be considered as typical of gastric ulcer, etc., only the average curve of the cases examined here.

In gastric neurosis we find that the amount of free hydrochloric acid bears a constant relation to the total acidity; that there is a slight increase in acidity, due probably in the fasting stomach to the stimulation of the tube, and then a gradual fall; that the mean free hydrochloric acid is 20, total acidity 40; that after an Ewald meal there is a gradual rise in the acidity for seventy-five minutes, and then a gradual decrease. The mean acidity was free hydrochloric acid 30, total acidity 60. In gastric ulcer the mean acidity is greater, and the curve fluctuates more, probably due to a fewer number of cases from which this curve was plotted.

In duodenal ulcer the acidity is greatest, and the stomach emptied itself sooner than in other conditions. In carcinoma and pernicious anemia there is a drop in acidity after passing the tube, both in the fasting secretions and after an Ewald meal, or else the total acidity remained constant.

There was no constant relation in the same individual between

the acidity curve of the fasting secretions and the acidity curve of the secretions obtained after an Ewald test meal. In most cases the acidity went higher after the Ewald meal. In some cases there was a descending curve for the fasting secretions and an ascending curve after a test meal.

A summary of the conditions observed in an investigation of the relation of the acidity curves in the fasting stomach and after an Ewald meal is as follows:

1. There is no curve which represents the normal acidity.
2. There is no curve which is typical of a certain pathologic condition.
3. There is no constant relation between the acidity curve of the fasting secretions and those obtained after a test meal in the same individual.
4. The average curve in carcinoma and pernicious anemia has a tendency to descend; in other conditions to ascend. The highest ascent was in duodenal ulcer.

DUODENAL ULCER

A diagnosis of duodenal ulcer was made only when no blood was found on the proximal side of the pylorus, and was found on the distal side, and in which the stool showed a positive guaiac on a benzidin-free diet. Roentgen ray was also used in most cases and showed a filling defect of the duodenal cap. There were only five such cases. From the subjective symptoms in other cases, the presence of a duodenal ulcer was suspected, but in the absence of any physical signs such a diagnosis was not made.

The gastric secretion of the fasting stomach showed, as a rule, a greater acidity than was found in other conditions. The color was not abnormal. The duodenal secretions, in addition to the presence of blood, contained an increased amount of exfoliated epithelium cells and white blood cells.

OBSTRUCTIVE JAUNDICE

Prior to the use of the duodenal tube here, a diagnosis of complete obstruction of the common bile duct was made when the patient was jaundiced, the urine contained bile pigments and no urobilin, and the stool did not show the presence of bile pigment or urobilin. Since using the duodenal tube here several such cases have been examined and all showed that bile was entering the duodenum, with the exception of two cases, in which no bile could be demonstrated.

The first case was in a woman, aged 56. Her health was good previous to October, 1913. At that time she began to have epigastric distress, flatulence, heartburn and occasional attacks of vomiting. January, 1915, she began to have cramp-like pains in the left hypochondrium, which radiated to the left

breast and shoulder. From then on she became jaundiced. She entered the hospital Sept. 3, 1915. Physical examination showed tenderness and rigidity over the region of the gallbladder. The liver edge was palpable 2 cm. below the costal margin. She was deeply jaundiced. A diagnosis of cholelithiasis was made, and on September 9 a laparotomy was performed. The gallbladder was distended and contained numerous small stones. It could not be emptied by pressure, although no stones could be palpated in the common duct. A cholecystostomy was done, and the stones were removed. The obstruction of the common duct could not be cleared without prolonging the operation beyond the limit of safety.

On October 7, one month after the operation, the patient's jaundice had decreased, the stool was clay-colored, the mercury bichlorid test for bile pigment was negative, and there was no urobilin in the stool. Hemoglobin was 65 per cent., red blood cells 3,400,000. The patient was much weaker than she was before the operation. The sinus into the gallbladder was still draining. The urine contained bile pigments and salts. The total nitrogen was 0.119 gm. per 100 c.c., and the ammonia nitrogen 0.01576 gm. per 100 c.c. The ammonia nitrogen was 1 per cent. The blood plasma also contained a large amount of bile pigment and bile salts.

An Einhorn duodenal tube was passed on a fifteen-hour fasting stomach. The secretion obtained on the proximal side of the pylorus was a clear, opalescent liquid, with a trace of mucus. There were no bile, and no blood. There was free hydrochloric acid 8, with a total acidity of 22. In one and one-quarter hours the secretion obtained had the same characteristics, with free hydrochloric acid 8, and total acidity 20. The bile test was doubtful. A quantitative test for trypsin showed a normal amount, thus proving that the obstruction was not at the papilla of Vater. The duodenal tube was left in for ten days, during which time 1 ounce of her own bile was collected from the incision, and fed through the tube with 6 ounces of milk and one egg, three times a day. In addition the patient ate a soft diet. At the end of this time she had gained in weight and strength. Her hemoglobin had come from 65 to 75 per cent. and her red blood cells were 4,672,000. Yet in spite of the fact that she had been getting 3 ounces of her bile every day, the stool remained absolutely acholic and no urobilin could be demonstrated. A cholecystenterostomy was then made. The patient made a complete recovery.

The only other case which showed a complete obstruction of the common duct was in a young man, whose only complaint was jaundice and malaise. No bile could be demonstrated in his duodenal secretions for three days. On the third day bile was obtained, which contained colon bacilli. On that day he felt better. The icterus began to disappear, the bile pigments and salts diminished in his urine, the stool contained bile pigments and in four days the amount of urobilin in the stool had increased. A diagnosis of catarrhal jaundice was made.

Three other cases showed all the signs of a complete obstruction of the common duct, namely, choluria, cholemia, icterus and acholic stools, except that the duodenal secretions contained bile. One was diagnosed syphilitic and alcoholic hepatitis. The secretions on the distal side of the pylorus were normal in color and acidity, but decreased in amount. Only 4 c.c. were obtained after aspirating for fifteen minutes. With antisyphilitic treatment the liver edge came from the level of the umbilicus to the costal margin in the nipple line, the jaundice disappeared and the urine and stool became normal.

The other cases were diagnosed cholelithiasis. One patient was operated on and a stone was found in a dilated common duct. The other patient refused operation and was discharged unimproved

CHOLELITHIASIS

The normal duodenal secretions contain no free hydrochloric acid. It is a clear, amber fluid, and remains amber for several days, gradually changing to a green color, as the bilirubin becomes oxidized to biliverdin. However, if hydrochloric acid is present it becomes of a cloudy yellow color, due to the precipitation of bile pigment by hydrochloric acid. A sediment forms on standing, which, microscopically, is seen as a fine, light-yellow detritus. The bilirubin becomes oxidized to biliverdin immediately after removal and often before, as evidenced by the green color.

The duodenal secretions found in four patients having more or less typical symptoms of gallstones contained a heavy sediment, which was different from that seen in other cases. It was heavier and of an orange yellow color. The duodenal secretions were cloudy. Microscopically the individual particles of detritus were larger and more highly colored than those precipitated by acid. It stained very poorly with methylene blue.

Three of these patients were operated on and the gallbladder was found to contain numerous small stones. The bile aspirated directly from the gallbladder presented the same microscopic picture. In one case there were only two or three hard stones, but a soft, putty-like detritus filled the bladder. The other patient is to be operated on this summer.

There are two possibilities as to the origin of this detritus. One is that the formed stones, by the peristalsis or contractions of the gallbladder and motion of the abdominal wall, grate against each other and thus produce the detritus. The other is that it is formed in the same manner as are the stones, the stones being larger and older. However, on finding an orange yellow, coarse detritus in the duodenal secretions, together with a history of colicky pains, or jaundice, a positive diagnosis of numerous gallstones can be made. No abnormal findings were present in the duodenal secretions in cases of cholelithiasis in which only one stone was present.

CHOLECYSTITIS

The normal duodenal secretion is a clear, amber-colored fluid. It becomes of a cloudy yellow color when free hydrochloric acid is present. When neutralized with sodium hydroxid it becomes clear again. An alkaline duodenal secretion that is cloudy is very suggestive of cholecystitis. The cloud is due either to bacteria or white blood cells. The addition of sodium hydroxid does not clear the fluid.

Some saliva is invariably swallowed. This saliva contains bacteria, white blood cells and desquamated epithelium. Therefore a few bacteria, pus cells and epithelium are always found in the secretions on the proximal and distal sides of the pylorus. Those elements present on the distal side of the pylorus are fewer in number, but morphologically the same as those found in gastric secretions. The first specimen removed from the stomach contains more bacteria and cellular elements than the succeeding specimens.

In inflammatory conditions of the stomach, duodenum and biliary tract, the number of white blood cells and exfoliated epithelium is increased. The epithelial cells from the stomach, duodenum and biliary tract are easily differentiated from the squamous epithelium from the mouth. They are oval and the cells are larger. McNeil[2] distinguishes the pus cells swallowed from those arising in the stomach or duodenum by the fact that the former are clumped in mucus, the latter are found free. McNeil also differentiates the epithelial and white blood cells of the biliary tract from those of the duodenum and stomach by the yellow color of the former. We have not made that differentiation, because, if a cover-slip preparation is made from duodenal secretions which contain pigmented epithelium and white blood cells, and then sodium hydroxid be added, while under observation the pigment dissolves out, leaving all the cells nonpigmented. Then while the preparation is still under the microscope, if dilute hydrochloric acid is added, the bile pigment is seen to precipitate and clump; some pigment is deposited on white blood cells and epithelium; and, further, in the normal clear, amber, duodenal secretion, none of the epithelial cells are stained, and some of the cells, no doubt, come from the biliary tract. The secretions on the proximal and distal sides of the pylorus were in most cases examined microscopically for bacteria. Cultures were made only when a motile bacillus was found, or when those found in the duodenum appeared different in number and type from those present in the gastric secretions. In a few cases colon bacilli were found in the duodenal secretions and not in the gastric secretions. In most cases there were no colon bacilli. An attempt was made to see if there was a constant level in the duodenum at which the colon bacilli were present. The tip was allowed to go into the duodenum the length of the tube, 90 cm. from the mouth and 30 cm. from the pylorus. Specimens were obtained every 10 cm. and cultures made. In general, colon bacilli were obtained more frequently the farther down in the duodenum the tip was. The distance from the pylorus that they appeared was not constant; the individual variations were great.

2. McNeil, H. L.: Am. Jour. Med. Sc., 1916, **151,** 906.

The typhoid bacillus was found in the duodenal secretions of one patient. He was a man about 49 years old. He entered the hospital complaining of some pain and distress in right hypochondrium. He had sensory disturbances on extremities, loss of vibratory sense and diminution of other sensations. Tenderness and rigidity in right hypochondrium. Physical examination, including the secretory and motor function of the stomach, spinal fluid and blood was negative. His duodenal secretion was slightly cloudy, the reaction faintly acid. Microscopic examination showed numerous motile bacilli, which were not present in the gastric secretions. Cultures were grown on slant agar. These were then plated. A motile organism was isolated, which caused no fermentation in dextrose, maltose, lactose or saccharose bouillon, thus proving to be the bacillus typhosus. His symptoms probably were due to a typhoid cholecystitis.

In December, 1915, a Japanese patient entered the ward with a diagnosis of bleeding duodenal ulcer. Physical examination revealed dulness at the right base. He had a very foul, putrid expectoration. Roentgen ray showed an opacity at the right base, probably a lung abscess. His abdomen was very rigid and tender, especially in the right hypochondrium. The liver edge was palpable and he was jaundiced. A large amount of dark blood was passed per rectum. This was found to be due to internal hemorrhoids. These were operated on and the hemorrhage ceased. A Rehfuss tube was passed on a fifteen-hour fasting stomach. While passing the tube the patient expectorated a large amount of yellow, fetid, purulent mucus.

TABLE 3.—Findings by Means of Rehfuss Tube in a Case of Gastritis, Duodenitis and Cholecystitis

Specimen	Time, Min.	Characteristics	Mucus	Free HCl	Total Acidity	Bile	Blood
1	..	.....	Too much mucus to titrate	...	..	0	0
2	25	Cloudy yellow	+++	0.4	20	+	0
3	35	Cloudy yellow	++	0	24	++	0
4	50	Clear amber	.....	0	20	+++	0

Microscopic examination of a second specimen showed a very large number of pus cells, both free and in clumps of mucus. The secretion consisted of a large amount of mucus. The mucopurulent secretion swallowed could be differentiated from the gastric secretion by the yellow color. There was a large number of bacteria, a large diplococcus predominating. There was also an increased amount of squamous epithelial cells.

Examination of the duodenal secretion showed an increased amount of mucus, but there was no blood. Microscopic examination showed a few white blood cells, which were not clumped in mucus. There were a few oval epithelial cells. Some were stained yellow and they contained a small coccus. There were numerous extracellular organisms resembling staphylococcus.

From the increased amount of mucus, white blood cells, desquamated epithelium and bacteria in the secretions, a diagnosis of chronic gastritis was made. From the same findings in the duodenum, namely, mucus, pus cells, bacteria, exfoliated oval epithelium, a duodenitis was shown to be present. From the presence of exfoliated oval epithelial and pus cells in the duodenal secretions, the jaundice, large liver and tenderness in the right hypochondrium a diagnosis of cholecystitis was made. The gastritis, duodenitis and cholecystitis was secondary to the pulmonary infection.

As a summary of the findings in cases of cholecystitis, the following points may be mentioned:

1. The normal alkaline duodenal secretion has a clear, amber color.

2. The presence of free hydrochloric acid produces a cloudy yellow duodenal secretion, which becomes clear when neutralized.

3. An alkaline duodenal secretion that is cloudy is suggestive of an inflammatory condition in the duodenum or biliary tract. The cloud is due to the presence of bacteria and pus. It does not clear on the addition of sodium hydroxid.

4. Epithelial and white blood cells, which are stained yellow by the bile pigment, do not necessarily come from the biliary tract. They may be stained while in the duodenum by the precipitation of bile pigment by the free hydrochloric acid from the stomach.

5. Colon bacilli are occasionally present in the duodenum. The level in the duodenum at which they appear varies.

PERNICIOUS ANEMIA

There have been two prevailing theories regarding the origin of pernicious anemia, since it was distinguished from other forms of anemia by Addison. Paul Ehrlich first set forth the theory of "a megaloblastic degeneration of the blood-forming structures," and W. Hunter gave the theory that the process was hemolytic, the origin to be found in a more or less specific affection of the gastro-intestinal tract.

In support of the hemolytic theory, the following discoveries are to be considered:

1. In 1907 Tallqvist showed that in degenerated parts of bothriocephalus, by an autolytic process a cholesterin ester of oleic acid was formed, and that this caused an anemia similar and often identical with the type known as pernicious anemia.

2. In small, nonulcerated cancer of the stomach there is often associated an anemia of megaloblastic type. From these growths Kullmann and Tallqvist have separated a hemolytic substance similar to that obtained in bothriocephalus.

3. Since pernicious anemia is usually associated with and often preceded by digestive disturbances, such as anorexia, gastric discomfort, achylia and periodic diarrhea, Grawitz believed enterotoxic products were formed from insufficient or faulty denaturation of the albuminates, the diarrhea and large amount of mucus being due to a nucleoprotein, formed from the intestinal epithelium.

4. Korshum and Morgenroth produced hemolytic lipoids from normal organs.

5. Berger and Tsuchuja, in two cases reported by Adolf Schmidt, extracted the lipoids from the mucosa of the whole intestinal tract. This they found to have ten times the hemolytic power of that obtained from the normal mucosa.

6. Pilcher, from a study of thirty-four cases of pernicious anemia in the Mayo Clinic, concludes that the achlorhydria resulted from chronic gastritis; that, due to the achlorhydria, the bacterial flora was markedly increased, from which toxins are formed. The absorption of toxins, together with the disturbance of digestion, impairs the formation of antibodies, until finally a bacteremia is produced, usually of streptococcus origin. This stage is recognized by the elevation of temperature and proved by frequently growing the streptococcus from the blood during the febrile period.

7. Experiments have shown that the blood in the peripheral circulation seldom shows signs of hemolysis, or increased fragility. In the portal venous system the excessive accumulation of iron in the liver and the reddish color seen in the portal lymph nodes are suggestive of a hemolytic agent in the portal circulation.

Considering the theory that pernicious anemia is caused by a hemolytic agent and that this agent is dependent on a disturbance of the gastro-intestinal tract, I attempted to find out if there were present in the gastric and dnodenal secretions any substance which had a greater hemolytic action than in normal secretions. The hemolytic power of the secretions on the proximal and distal sides of the pylorus was determined on six patients who were not anemic. Another series of six tests on six patients suffering with pernicious anemia was done.

Technic: Into a series of test tubes was placed 5 c.c. of normal saline. Into the first tube 5 c.c. of filtered, fasting gastric or duodenal secretions was added and the contents mixed. Then 5 c.c. of the mixture in the first tube was added to the second tube, which in turn was mixed and the process repeated. This made dilutions of 1 to 1, 1 to 2, 1 to 4, 1 to 8, etc. To each tube 1 c.c. of oxalated, washed red blood corpuscles was added. A control of normal saline and the blood was always made to make sure no hemolysis took place and the presence of oleic acid ruled out. The amount of hemolysis was noted at intervals during twenty-four hours.

The result of this series showed, without a single exception, that the gastric and duodenal secretions from cases of pernicious anemia caused no more hemolysis than do normal secretions.

CONCLUSIONS

1. The secretory and motor function of the stomach can best be determined by the fractional method of examination.

2. The normal alkaline duodenal secretion is of a clear, amber color. The presence of free hydrochloric acid precipitates the bile pigments and it becomes of a cloudy yellow color, which will become clear again when neutralized.

3. A cloudy duodenal secretion that is alkaline is significant of an inflammatory condition in the gallbladder, bile ducts, duodenum or stomach. The cloud is due to bacteria and pus. It does not clear on the addition of sodium hydroxid.

4. A detritus that is typical in appearance may be found in the duodenal secretions in cases of cholelithiasis, when there are numerous small stones.

5. An absence of bile pigment and urobilin in the stool is not proof that there is no bile entering the duodenum.

6. Three ounces of bile may be given every day into the duodenum and the stool still give a negative test for bile and urobilin.

7. The secretions on the proximal and distal sides of the pylorus from cases of primary anemia cause no greater hemolysis of red blood corpuscles than the secretions obtained from patients who are not anemic.

THE RELATION OF HYPERTROPHIC OSTEO-ARTHROPATHY TO PULMONARY TUBERCULOSIS *

LEO KESSEL, M.D.
NEW YORK

Cases of hypertrophic pulmonary osteo-arthropathy have been presented to this section by Dr. Theodore Janeway and our present secretary, Dr. Brooks. My excuse for bringing the subject to your attention is to emphasize certain points in the relation of this interesting clinical condition to pulmonary tuberculosis.

The relative rarity of osteo-arthropathy in association with pulmonary tuberculosis has been mentioned by several authors. The writer of one of our modern textbooks on tuberculosis states that he has examined 2,300 patients suffering from pulmonary tuberculosis without once having encountered an osteo-arthropathy. It is only within the past decade that the importance of pulmonary tuberculosis as an etiologic factor in hypertrophic osteo-arthropathy has been recognized. The literaure to date contains about forty-three cases. Considerable discussion has appeared from time to time regarding the relation of club fingers to hypertrophic osteo-arthropathy. A number of French and a few German authors believe that the one bears no relation to the other; but frequently this decision has been reached on insufficient evidence. Bamberger,[1] Marie,[2] and Lefebvre[3] believed both conditions to be similar phenomena. Janeway[4] regarded them as different stages of the same process, and suggested thirteen years ago that careful radiographic observation of the distal ends of the radius and ulna might show slight thickenings in many cases of simple hippocratic fingers.

* Submitted for publication June 23, 1916.
* Read before the Section on Medicine of the New York Academy of Medicine, May 16, 1916.
* This work was carried out in the wards of the Montefiore Hospital for Chronic Diseases.

1. Bamberger, E.: Ueber Knochenveranderungen bei chronischen Lungen und Herz Krankheiten, Ztschr. f. klin. Med., 1891, **18,** 193.

2. Marie, P.: De l'osteoarthropathie hypertrophiante pnuemique, Rev. de méd., 1890, **10,** 50.

3. Lefebvre, A.: Des déformations ostéo-articulaires consécutives à des maladies de l'appareil pleuro-pulmonaire, Thèse de Paris, 1891.

4. Janeway, T.: Hypertrophic Osteo-Arthropathy; with Report of Two Cases, Am. Jour. Med. Sc., October, 1903.

In a comprehensive paper published one year ago Dr. Edwin Locke[5] of Boston demonstrated very clearly that simple clubbing of the fingers and hypertrophic osteo-arthropathy were identical, the former representing an early stage of the latter.

It is usually conceded that prolonged venous congestion is the cause of the ordinary clubbed fingers, and Brooks,[6] quoting Ziegler, has pointed out that a continued peripheral hyperemia is produced by compression of the lung capillaries in pulmonary, pleural or mediastinal disease, and that in the course of time this hyperemia induces a

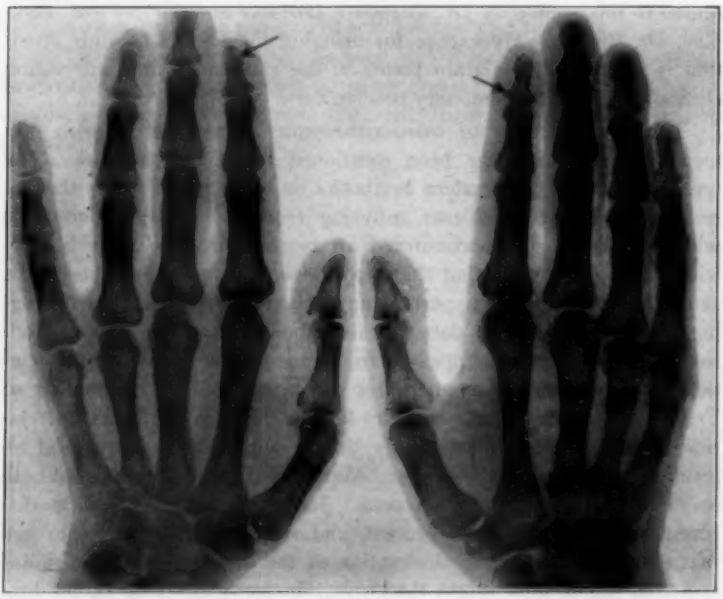

Fig. 1.—Marked increase in the soft tissues of all of the end phalanges. The tips of the distal phalanges present a distinct cauliflower-like formation, and the bases are quite markedly widened, owing to small bony projections. The middle phalanges appear unusually short and their bases are broadened.

hyperplasia in the periosteum and connective tissue. A circulating toxin, the product of the primary disease, probably plays a rôle in producing the bone changes in many cases, and its action appears most apparent where venous stasis has been marked and prolonged.

5. Locke, E.: Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club-Fingers, THE ARCHIVES INT. MED., 1915, **15**, 659.

6. Brooks, Harlow: The Etiology of Hypertrophic Pulmonary Osteo-Arthropathy, New York Med. Jour., Sept. 27 and Oct. 4, 1913.

The underlying changes in the soft tissues of the fingers and toes have been generally described as a connective tissue hyperplasia, with capillary dilatation. The essential pathologic features of the bone disease consist in a progressive, ossifying periostitis, usually manifesting itself in the distal ends of the diaphyses of the long bones of the arms and legs, and later involving the other bones of the skeleton. In long-standing cases the changes in the periosteum may involve all of the bones, including the cranial bones. These bone changes in advanced

Fig. 2.—The soft tissues of all the toes are increased and the tips of the distal phalanges of the great toes show an exaggeration of a burr-like formation. The fifth metatarsal bones appear at their inner aspect to be lined with a thin layer of new bone, perfectly regular in outline, and showing a sharp line of demarcation between the new bone and cortex.

stages of the disease are not necessarily confined to the diaphysis, but, as Locke has shown, the epiphyseal portions may produce new bone formation. We were unable to demonstrate this in any of our roentgenograms, but none of our patients presented so pronounced a picture of the disease as some of those described by Locke.

Patients presenting evidence of hypertrophic osteo-arthropathy vary markedly in their clinical manifestations of the disease. Some

show simple hypertrophy of the soft tissues about the terminal phalanges, with thickening and cyanosis of the nails, which are at times parrot beak in shape; others, in addition to this clubbing, display an enlargement of the hands and feet, and a thickened, clumsy appearance of the lower forearms and lower legs. When the disease is well developed, the normal tapering appearance of the lower forearms and lower legs is completely lost, the periarticular thickening is marked, and the joint involvement pronounced. The patients sometimes complain of

Fig. 3.—Apparent increase of soft tissues about the terminal phalanges. The tips of these phalanges show a burr-like formation. The fifth metatarsal bones present a distinct layer of new bone, about 0.2 cm. in width, on the internal aspect.

considerable pain in the bones and joints involved and examination often shows these parts to be quite tender.

A point mentioned by the earlier writers and well emphasized by Brooks is the tendency in these patients to the formation of a globular nose and distinct evidence of thickening of the subcutaneous tissue in the malar regions. These marks of peripheral stasis occurred quite prominently in our series of patients, the changes in the nasal tip being present in twelve patients, and the malar thickening appearing in nine of them.

The thirty-two patients to be reported on were gathered from a service of about 100 patients suffering from pulmonary tuberculosis. They were all in the second or third stage of the disease. Roentgen examinations were made of the hands, feet, all of the long bones, the bones of the pelvis, and in some instances the shoulder girdle and cranial bones. Following the classification made by Locke, we have divided these thirty-two patients into three groups (Tables 1, 2 and 3):

Fig. 4.—The fifth metatarsal bones show on their inner aspect a thin layer of new bone about 0.2 cm. at their broadest point. A sharp line of demarcation separates the new bone from the cortex of the metatarsal.

(1) five patients presenting simple, well-defined clubbing of the fingers without bone changes; (2) seventeen patients showing clubbing of the fingers with bone changes in the phalanges; and (3) ten patients with clubbed fingers and changes in the long bones.

Of the five patients in Group 1, namely, those presenting simple clubbing of the fingers, three were men and two women. They varied in age from 19 to 42 years, and the length of illness ranged from one

to six years. Extensive pulmonary cavitation was present in three of these patients (M. V., S. L. and J. M.). It is noteworthy that the patient J. M., who had been ill six years, first noticed a change in the appearance of her fingers three and a half years ago. Roentgen-ray examination, made only one month before her death, failed to demonstrate the slightest change in any of her bones, in spite of the presence of an extensive pulmonary lesion, which, during the last year of her life, had produced dyspnea, toxemia, and long periods of continued fever. The patient M. V. presented a similar history, extending over a shorter period, with the same negative Roentgen-ray findings.

Fig. 5.—Section of lower end of radius from patient I. G., showing a dense layer of new bone formation separating the periosteum from the cortex.

Of the seventeen patients in Group 2, fourteen were men and three women. The ages varied from 18 to 63 years, and the length of illness from one to six years.

The appearance of the patients in this group differed in no way from those in Group 1. They presented various degrees of clubbing of the terminal phalanges of the fingers and toes, but the Roentgen-ray examination disclosed changes in the bones of the hands and feet not seen in those of Group 1. The bone changes consisted in cauliflower-like excrescences of the tips of the end phalanges, with point-like projections of the bases of those phalanges. At times these projections appeared as true osteophytes. The middle phalanges were short, thick and broadened at the base (Fig. 1).

The Roentgen-ray examination in three of these patients showed a layer of new bone formation along the lateral or internal aspects of the fifth metatarsal bones (Figs. 2, 3 and 4). In the patient D. H. section of the fifth metatarsal proved the inner layers of the periosteum to have been invaded by a new bone formation, the new tissue differing from the old bone in that the osteoblasts were few in number and showed no lamination (Fig. 5).

Fig. 6.—The fifth left metatarsal bone presents at its lateral aspects a thin layer of new bone, showing in some places a distinct line of demarcation. This line disappears entirely at the middle portions, where the normal differentiation between the cortex and medullary layer has disappeared.

All of the patients in Group 3 were men. The age range was between 25 and 43 years, and the length of illness from less than one to eleven years.

In three of these patients the lower ends of the forearms and lower portions of the legs were markedly thickened and clumsy in appearance. In two of these patients the thickened areas were distinctly tender. Although one patient complained of pains in his wrists and ankles, there was no apparent change in the joints of any.

Six patients of the ten in this group presented the globular nose formation and malar thickening. With the exception of the awkward appearance of the lower arms and legs in the three patients just described, the patients in Group 3 disclosed nothing in their physical examination to differentiate them from patients in either of the other two groups, yet the Roentgen-ray examination revealed decided differences. Nine of them showed changes in the phalanges similar to those described as characteristic of Group 2. A layer of new bone

Fig. 7.—The upper third of the femur shows a thick layer of dense and well-differentiated new bone at the lateral and external aspect.

formation on either the inner or outer aspect of the fifth metacarpal or metatarsal bone was evident in six patients of this group (Fig. 6). We were unable to determine an anatomic basis for the appearance of this new subperiosteal bone formation in the fifth and not in any of the other metacarpal or metatarsal bones.

All of the patients in this group showed more or less marked changes in the bones of the forearms and legs, and in three patients the

femora were involved (Fig. 7). The subperiosteal layer of new bone, usually about 0.5 cm. in thickness, appeared at the epiphyseal line or just above and extended upward for varying distances (from 4 to 10 cm.), in most instances showing a sharp line of demarcation from the cortex (Figs. 8, 9 and 10). In other patients the layer of new bone merged at points with the old, and in some a lack of differentiation between the cortical and medullary layer of the bone proper was

Fig. 8.—Layer of new bone just above the styloid process of the ulna and extending upward about 4 cm.

evident (Fig. 11). Plates taken in several positions demonstrated that this layer of subperiosteal new bone appeared on the various aspects of the bone involved.

One of these patients (A. G.) showed marked clubbing of his fingers without changes in the distal phalanges, but a distinct layer of subperiosteal new bone was demonstrated in the ulna, tibia and fibula. Such findings emphasize the importance of Roentgen-ray examinations

of the long bones, even in those cases which fail to reveal pathologic conditions in the phalanges; and they are also of aid in correcting many of the earlier misconceptions regarding the pathogenesis of this condition.

We sought in this whole series of patients to establish some relation between the clinical manifestations of the pulmonary disease and the type of osteo-arthropathy present, but we have been unable to demonstrate a connection between the two.

Fig. 9.—Both femora present symmetrical changes consisting of a layer of new bone at both lateral aspects, beginning just above the condyles and extending upward on the external side about 5 cm. and on the internal side about 3 cm.

A study of the tables will show that pronounced evidence of pulmonary tuberculosis may be associated, on the one hand, with simple clubbing of the fingers, while, on the other hand, less marked manifestations of the pulmonary disease may be accompanied by distinct changes in the long bones. The bone changes, moreover, are not definitely associated with the type or degree of the clinical expression of the pulmonary disease.

Very few reports of metabolic studies of patients suffering from hypertrophic osteo-arthropathy have appeared in the literature. Through the courtesy of Dr. Brooks we were enabled to investigate the metabolism in the patient exhibited by him before this section in 1911. This patient presented a very advanced type of the disease, so that we thought if a perversion of metabolism existed in osteo-arthropathy, it could easily be demonstrated in this patient. A careful

Fig. 10.—The ulna shows at its external aspect a fine layer of new bone formation, extending from the styloid process upward about 3 cm. Practically the same change is seen at the external aspect of the radius.

study of his nitrogen and calcium metabolism, carried out for one week by Dr. Janney, failed to show a deviation from normal standards.

When we studied these three groups of patients in connection with the Roentgen-ray examinations, certain facts became evident:

1. The degree of clubbing corresponds only in a general way to the radiographic findings.

2. Bone changes occur more commonly than is ordinarily supposed in the so-called simple-clubbed fingers.

3. Pronounced changes in the long bones may take place without any clinical sign or symptom being present.

4. Systematic Roentgen-ray examinations reveal such changes.

Fig. 11.—Dense layer of new bone lining both lateral aspects and extending upward above the malleoli about 6 cm. The normal line of differentiation between the cortical and medullary bone has to a great extent disappeared at the lower end of the tibia and fibula.

5. The type of bone change in the various groups is the same, the difference being rather in the degree.

6. Hypertrophic osteo-arthropathy is present more frequently in pulmonary tuberculosis than the usual clinical examination would permit us to believe.

GROUP 1.—FIVE PATIENTS PRESENTING SIMPLE, WELL-DEFINED CLUBBING OF THE FINGERS WITHOUT BONE CHANGES

CASE 1 (No. 27922).—H. L., aged 32 years, a Russian, presented a lung condition dating back two years and beginning with a sudden hemoptysis. He was in the third stage of an afebrile course, with the sputum positive.

The index and middle fingers of the left hand showed a fair amount of clubbing with curved nails. He did not complain of any joint pains, nor was he aware of his digital abnormalities.

The Roentgen-ray report on the bones showed that there is a distinct increase in the soft parts of all the fingers, most marked at the tips and around the interphalangeal joints. There was also marked increase in the soft parts of all the toes, but there were no bone changes in hands, feet, arms or legs.

CASE 2.—M. V., a man, aged 42 years, an Austrian, a cutter by occupation, was examined Nov. 23, 1915, and presented a lung condition which dated back two years. He was in the third stage with the sputum positive, and the disease was running a febrile course. Both upper lobes were infiltrated and moist râles were present. The disease was complicated by the loss of the superficial epithelium of the right false vocal cords and perforation of the lower quadrant of the left ear drum. The patient had never noted any changes in the distal ends of the extremities until his attention was called to it. The heart was slightly dropped.

TABLE 1 (GROUP 1).—FIVE PATIENTS PRESENTING SIMPLE CLUBBING OF FINGERS AND TOES

Name	Age, Yr.	Years Ill	Stage	Fever	Dyspnea	Toxemia	Cough	Expectoration
H. L.	32	2	3	0	Marked	Moderate	Marked	Marked
M. V.	42	2	3	+	Marked	Marked	Severe	Profuse
S. L.	23	6	3	+	Marked	Slight	Severe	Profuse
D. H.	19	1	2	Slight	None	Slight	Moderate	Moderate
J. M.	23	6	3	+	Marked	Marked	Marked	Profuse

The finger nails were moderately curved and showed longitudinal striations and some thickening. There was slight enlargement of the distal phalanges as a whole. These changes were still more marked in the feet, more particularly in the great toes, in which the thickening of the soft tissue was very evident.

The Roentgen-ray report did not show any pathologic changes in the terminal phalanges or other bones of the hands, feet, arms or legs.

CASE 3.—S. L., a Russian woman, aged 23, a milliner by occupation, presented a lung condition which dated back six years. Both upper lobes were infiltrated with evidences of activity throughout both lungs. The patient was in the third stage of the disease, which was running a febrile course. The sputum was positive.

The patient had had no pain in any of the joints of the extremities. She did not remember having noted any change in the distal ends of the extremities. The nails of the fingers were thickened, somewhat parrot beak in shape, and the fingers and toes were slightly clubbed.

The Roentgen-ray report showed no pathologic changes in the bones of the hands, feet, arms or legs.

CASE 4.—D. H., a newsboy, aged 19 years, born in the United States, showed a pulmonary condition which dated back one year. He also suffered from a cardiac disturbance necessitating his stay in bed. His pulmonary disease was

in the third stage, and the sputum was positive. The disease was running an afebrile course.

There was slight curving of the nails and very slight thickening of the soft tissue, with similar changes, but more marked, in the toes, particularly in the great toes.

The Roentgen-ray report showed that there was apparent increase in the soft tissue of the hands, but no bone changes in the hands or feet. The forearms, arms, legs and femora were negative.

CASE 5.—J. M., a woman, aged 23, showed a pulmonary condition which dated back six years. She was in the third stage, running a febrile course, with the sputum positive.

The disease was complicated by tuberculous enteritis, laryngitis and nephritis.

The patient first noticed changes in the shape of her fingers and toes about three and a half years before examination. She had had no pain in any joints until a short time before examination. The pains she complains of were only of the toes, ankles and feet, probably due to the pressure exerted by the edema present. There was slight curving of the nails and clubbing of both the fingers and the toes.

The Roentgen-ray report showed that the marked increase was in the soft tissues of the fingers and toes, but that there were no bone changes in the hands, feet, arms or legs.

GROUP 2.—SEVENTEEN PATIENTS SHOWING CLUBBING OF THE FINGERS, WITH BONE CHANGES IN THE PHALANGES

CASE 1 (No. 25610).—S. K., a man, aged 55 years, a pedler by occupation, was examined Nov. 23, 1915, and gave a pulmonary history dating back four years. He was in the second stage of an active process, usually afebrile. There was emphysema, and the sputum was positive.

He had had no pain in any of the joints, but he had noticed a slight clubbing of the fingers and curving of the nails about twelve years before, which gradually became more marked as the pulmonary disease progressed.

There was a slight clubbing of the fingers and curving and thickening of the finger nails, particularly of those on the right hand, also a slight enlargement of all toe tips and curving of the toe nails. There was apparent enlargement of the nasal tip, which was somewhat globular in shape.

The Roentgen-ray report showed cauliflower-like growth of the tips of the terminal phalanges, and Heberden's nodes were present, but there were no other pathologic changes in the bones of the extremities.

CASE 2 (No. 29158).—J. M., a man, aged 27, a salesman by occupation, was examined Aug. 19, 1915, and showed a pulmonary condition which dated back about three years. He was in the second stage, with both upper lobes of the lungs infiltrated, and the sputum positive.

He had not had pain in any joint, and did not remember when the joint enlargement began. The only enlargement of joints was found in the distal ends of the phalanges. These were slightly clubbed, with thickening of nails, which were also slightly curved.

The Roentgen-ray report showed marked cauliflower formation at the tips of all the end phalanges of the hands. Distinct bony excrescences were visible at the bases of the middle and end phalanges of the second, third, fourth and fifth fingers on both sides, giving those basal portions a broadened, somewhat fan-shaped appearance. There were a few minute arthritic changes at some of the distal interphalangeal joints. The feet, legs and forearms gave no definite evidence of any pathologic changes in any of the bones.

CASE 3 (No. 31071).—J. L., a tailor, aged 51, showed a pulmonary condition which dated back one year. He had had no pains in the joints or the long bones. He had at the time of examination pains in both calves, but he had had no rheumatism or sore throat. There were distinct curving and thicken-

ing of his nails and slight hypertrophy of the soft parts of his finger tips, with marked thickening and curving of the nails of the toes.

Both upper lobes of the lungs were dull, with no apparent excavation. He was running an occasionally febrile course, and he had had pulmonary hemorrhages at times. He was in the second stage, with sputum positive. The heart was small, somewhat dropped, and there was moderate bulging of the right wall of the ascending aorta.

The Roentgen-ray report showed that the tips of the end phalanges of the hands had an exaggeration of burr-like excrescences, and their bases had point-like projections which might be called abnormal. There was a moderate amount of cystic degeneration at the tips of the end phalanges. The forearms, arms and lower extremities were negative.

TABLE 2 (Group 2).—Seventeen Patients Presenting Simple Clubbing of Fingers or Toes with Changes in the Distal Phalanges

Name	Age, Yr.	Years Ill	Stage	Fever	Dyspnea	Toxemia	Cough	Expectoration
S. K.	55	4	2	At times	Moderate	Slight	Marked	Profuse
J. M.	27	3	2	At times	Moderate	Slight	Moderate	Moderate
J. L.	51	1	2	Very slight	0	0	Moderate	Moderate
M. E.	42	3	3	+	+	+	Severe	Profuse
J. F.	63	4	3	Slight at times	+	+	Severe	Profuse
J. J.	29	2	3	Slight	0	Slight	Moderate	Moderate
E. B.	34	4	3	Slight at times	0	0	Moderate	Profuse
T. R.	40	2	3	At times	Slight	Slight	Severe	Profuse
M. B.	18	1½	3	+	+	+	Severe	Moderate
J. S.	50	4	3	At times	0	0	Slight	Very moderate
S. J.	37	1	3	+	+	+	Severe	Profuse
D. H.	45	2	3	+	+	+	Severe	Profuse
N. S.	45	5	3	+	Slight	Moderate	Severe	Profuse
M. C.	42	3½	3	0	Slight	Moderate	Severe	Profuse
I. S.	30	2½	3	At times	0	Slight	Severe	Profuse
A. S.	39	3	3	+	+	+	Severe	Profuse
P. M.	23	6	3	Slight	Slight	Slight	Moderate	Moderate

Case 4.—M. E., a Russian, aged 42 years, a hatter by occupation, showed a lung condition which dated back three years. He was in the third stage of pulmonary tuberculosis, which was complicated by laryngitis and hemoptysis. The sputum was positive, the course of the disease febrile.

He had noted no change in the appearance of his finger tips, nor had he experienced any joint pains. The nasal tip was thickened, and there was well-marked clubbing of his thumbs. This was less evident in the other fingers.

The Roentgen-ray examination showed that not only were the soft parts of all the fingers greatly increased, but the bony parts showed very marked cauliflower excrescences at the tips of the end phalanges and marked point-like projections of the basal portions of the same phalanges. The middle phalanges appeared short, thick, and markedly broadened at the basal portions. The forearms, feet and legs were negative.

Case 5.—J. F., a Russian, aged 63, a ragpicker by occupation, was examined Oct. 1, 1915, and showed a lung condition which dated back four years. He

was in the third stage, with the sputum positive, and the disease running an afebrile course.

Attention was first drawn to the clubbed condition of the finger tips about two years before, and this had afterward increased. He had no pains in the fingers. Both hands showed the same condition. The joints had never been painful. Examination revealed well-marked clubbing and incurving of the nails of all the fingers and of the second right toe and the first and second toes of the left foot. The patient complained of pains over lowest portion of the sternum on pressure. There was also marked thickening of the nasal tip.

Roentgen-ray examination showed a moderate amount of burring at the tips of the terminal phalanges. Point-like osteophytes were seen at the bases of most of the middle and end phalanges. There were beginning arthritic changes at some of the middle and distal interphalangeal joints, most marked in the fifth fingers. The feet, leg and forearms showed no definite bone changes. There was a beginning arteriosclerosis.

Case 6.—J. J., a Russian, aged 29, a woodcarver by occupation, showed a condition which dated back two years. He was in the third stage, the sputum was positive, the course febrile. The finger tips were moderately clubbed and the nails were curved; the toes were negative.

By Roentgen-ray examination the tips of the end phalanges of almost all the fingers showed a moderate amount of cauliflower formation. The basal portions of the end and the middle phalanges showed a point-like excrescence. The forearms, arms, feet and legs were negative.

Case 7.—E. B., a Russian, aged 34, a musician by occupation, gave a pulmonary history which dated back to March, 1912, when he began to expectorate blood-streaked sputum. He was in the second stage, the sputum was positive, and the course of the disease was afebrile. The finger tips show a fairly well-marked clubbing and incurving of the nails of both hands. The patient was not aware of this until his attention was called to it. The fingers, as a whole, looked rather short and thick. The nose was globular, and there was a thickening of the subcutaneous tissue in the malar region. The toes were similarly affected, but to a lesser degree. At no time had there been pain in the joints or extremities.

The Roentgen-ray report, made Sept. 8, 1915, showed a moderate amount of burring at the tips of all the end phalanges of the hands. There was a slight tendency to Heberden's node formation. The feet showed a moderate, irregular thickening of the cortical layer at the outer aspect of the upper third of the second left metatarsus, about one inch in extent. The legs and forearms gave no evidence of any gross bony lesion.

Case 8 (No. 31309).—T. R., a Russian, aged 40, suffered with an illness which dated back two years. He was in the third stage of pulmonary tuberculosis, running a febrile course, and the sputum was positive. There was a tendency to globular nose, but no malar thickening. The nails were curved, slightly cyanosed and somewhat thickened. There was marked thickening of the soft tissue of the terminal phalanges of the hands. The changes in the feet were similar, but less marked than in the fingers.

The Roentgen-ray examination showed that there was marked increase of all the soft parts in the fingers, most marked at the end phalanges. The bony parts showed a distinct broadening at the basal portion of the middle and distal phalanges. Most of the interphalangeal joints showed a distinct narrowing of the articular clefts. There were no bone changes in the arms, feet or legs.

Case 9 (No. 30389).—M. B., a Russian, aged 18 years, was examined Aug. 30, 1915. The patient's lung condition dated back one and one-half years. He was in the third stage of pulmonary tuberculosis, with positive sputum, and running a febrile course. There was an increase in the soft tissue of the fingers and a distinct thickening of the soft parts of the toes.

The Roentgen-ray examination showed that there was marked increase in the soft tissues of all the end phalanges of the hand, with the beginning of cauliflower formation and cystic degeneration in the bony tips. The forearms, arms, feet and legs were negative.

CASE 10 (No. 30407).—N. S., a man, aged 45 years, a cleaner by occupation, presented a pulmonary condition which dated back five years. At no time had he had pain in any of the joints, and he did not remember when the joint enlargement began. He was in the third stage of pulmonary tuberculosis, complicated by laryngitis, running a febrile course. The sputum was positive. There was marked thickening of the nails with longitudinal striations and parrot beak curving and hypertrophy of the soft tissues.

The Roentgen-ray examination, made Sept. 24, 1915, showed the hands with very marked cauliflower formation at the tips of all the phalanges. The basal portions of most of the terminal and some of the middle phalanges showed slight osteophyte formation. Most of the middle and terminal phalanges presented a peculiar fan-shaped appearance. The feet, legs and forearms showed no definite bone changes.

CASE 11 (No. 28386).—M. C., a Russian, aged 42 years, a painter by occupation, showed a pulmonary condition which dated back three and one-half years. He was in the third stage of pulmonary tuberculosis, running an afebrile course. The sputum was positive. There was slight thickening of the nasal tip and the subcutaneous tissue of the malar region. There were also distinct thickening and curving and longitudinal striations of the finger nails, and moderate thickening of the soft tissue, with similar changes in the toes.

The Roentgen-ray examination showed that there was a marked increase of the soft tissues in all the fingers, most marked in the tips, which also had an exaggerated cauliflower appearance. The bases were broadened, due to lateral excrescences, and the middle phalanges appeared somewhat shortened and thickened, due to an enlargement of the basal portions. The forearms and arms were negative. The soft tissues of the big toe were distinctly increased and the tips of the end phalanges showed marked burr-like excrescences. The legs were negative.

CASE 12.—A. S., an Austrian woman, aged 29 years, houseworker, showed a condition which dated back three years. She was in the third stage of pulmonary tuberculosis, running a febrile course. The sputum was positive. The patient had not noted a change in any of her fingers or toes, nor did she ever complain of any pain in the bones or joints. There was slight curving of the nails and clubbing of the finger tips, but there were no similar changes in the toes.

Roentgen-ray examination showed that the soft parts of all the fingers were markedly increased, especially at the end phalanges and around the interphalangeal joints. The bony parts presented very marked cauliflower formation at the tips of the end phalanges, marked broadening of the nasal portions of the same phalanges, due to bone excrescences. The basal portions of all the middle phalanges showed marked increase in width. All the other bones of the lower extremities failed to show any abnormality.

CASE 13 (No. 32783).—P. M., aged 23 years, a clerk, born in the United States, showed a pulmonary condition which dated back six years. He was in the third stage of pulmonary tuberculosis. The nasal tip showed some thickening. There was distinct curving and thickening with cyanosis of the finger nails, and moderate clubbing of the finger tips. There was very slight curving of the toe nails, with cyanosis; some thickening of the soft tissues of the tips, but they were not distinctly clubbed. There was no thickening or deformity of the long bones.

Roentgen-ray examination showed a moderate amount of bony overgrowth at the tips of the distal phalanges, with slight point-like projections at the bases of the same phalanges. There were no bone changes in the feet, arms or legs.

CASE 14.—I. S., a housewife, aged 30 years, an Austrian by birth, gave a pulmonary history which dated back two and one-half years. She was in the third stage of pulmonary tuberculosis, which was running a febrile course. The sputum was positive. There was no history of pain in any of the joints. There was slight clubbing of the fingers.

Under Roentgen ray the basal portions of most of the phalanges of the hands showed fine point-like projections. The fifth metatarsal bones showed a distinct irregularity in outline along both lateral aspects, extending almost throughout the entire shaft. This condition is symmetrical. The forearms, arms, legs, femora, hips and pelvis were negative.

CASE 15 (No. 31464).—D. H., aged 45 years, a tinsmith by occupation, gave a pulmonary history dating back to July, 1914. He was in the third stage of pulmonary tuberculosis, complicated by acute tuberculous pneumonia, tuberculous ulcer of the tongue, and tuberculous laryngitis. The sputum was positive. There was marked thickening and curving of the finger nails and a moderate hypertrophy of the soft tissues of the fingers. There were similar but less marked changes in the toes.

Roentgen-ray examination showed that the soft parts of all the fingers were moderately increased and the tips of the end phalanges showed quite a marked cauliflower appearance. The fifth metacarpal bones presented marked irregularity at the external and lateral aspects of the shaft, due apparently to irregularly formed layers of new bone. The forearms, feet and legs were negative.

The pathological report gave an anatomic diagnosis of calcified mediastinal lymph gland, chronic ulcerative pulmonary tuberculosis, proliferative miliary tubercles (lung), chronic and acute tuberculous pleuritis, acute tuberculous pneumonia, tuberculous laryngitis, tuberculosis of epididymis and seminal vesicle, tuberculous ulcer of tongue, tuberculous ulcer of colon, anemia and emaciation, fat deposits in the liver and pulmonary edema.

Microscopically a metatarsal section showed the inner layers of the periosteum invaded by new bone. This tissue differed from the old bone in that the matrix stained blue, the osteoblasts were few in number and showed no lamination.

The pathologic work in connection with this study was performed by Dr. Klein in the pathologic department of the Montefiore Hospital for chronic diseases.

CASE 16 (No. 30482).—S. J., aged 27 years, a tailor by occupation, gave a pulmonary history dating back one year. He had had no pain in any of the joints nor had he noticed any change in appearance of his fingers or toes. He was in the third stage of pulmonary tuberculosis and was running a febrile course. The sputum was positive. There was moderate thickening and curving of the finger nails and slight cyanosis. All the nails showed longitudinal striations and the finger tips showed thickening. Similar changes were evident in the toes. There was no enlargement or tenderness of the lower ends of the arms or legs.

Roentgen-ray examination, made Sept. 27, 1915, revealed a moderate amount of cauliflower formation at the tips of the terminal phalanges. There was some tendency to Heberden's node formation and some broadening of most of the middle and end phalanges. The feet were negative. There was marked irregularity in outline of the lower end of the right radius, and separation of the styloid process of the right ulna, due apparently to an old Colles' fracture of this process. The legs gave no evidence of any gross bony lesion.

CASE 17 (No. 29600).—J. S., a man, aged 50 years, a furrier by occupation, gave a pulmonary history dating back four years. He was in the third stage of pulmonary tuberculosis, running an occasionally febrile course. The sputum was positive.

For the previous two years the patient had occasional pains in his shoulder joints. These became constant during the previous year. Five years before

he had some throat trouble, with a constant burning pain. This had disappeared about two years before examination. He had never noticed a changed appearance of his fingers or toes. There was a thickening of the tip of the nose and of the subcutaneous tissue of the malar region, also clubbing of the fingers as well as slight enlargement of all the toes.

Under Roentgen ray the tips of all the end phalanges of the hands showed an amount of cauliflower formation, and the basal portions were broadened, due to point-like bony excrescences.

The fifth metacarpal bones, especially on the right side, showed marked irregularity and thickening of the cortical portions of the shaft at the lateral and external aspect. The forearms, feet and legs showed no definite abnormalities.

GROUP 3.—TEN PATIENTS WITH CLUBBED FINGERS AND CHANGES IN THE LONG BONES

CASE 1 (No. 29294).—S. S., aged 43, a peddler by occupation, gave a pulmonary history dating back four years. He had never had pain in any of the joints, but he had had pains in the soles of his feet. He was in the third stage of pulmonary tuberculosis, which was running a usually afebrile course. The sputum was positive. There was distinct thickening and slight cyanosis of the finger nails. The thumb nails were markedly curved and showed deep longitudinal striations. The tips of distal phalanges showed a cauliflower-like formation. The bases of the terminal and second phalanges were broadened. The forearms were negative. The feet failed to show any definite change. Both tibiae showed a dense layer of new periosteal bone extending from the malleolus region upward along the lateral aspect of the shaft about 4 cm., appearing quite well differentiated from the bone proper almost throughout the entire extent.

CASE 2 (No. 29997).—L. C., aged 39, a tailor by occupation, showed a pulmonary condition which dated back about eleven years. He was in the third stage of pulmonary tuberculosis, which was running a usually afebrile course. The sputum was positive. The disease was complicated by perforation of drum of left ear, nephritis and right inguinal hernia. The patient had never noticed any changes in the shape of the distal ends of his fingers or toes. He had complained of pains in his wrists, carpal, metacarpal, and phalangeal joints, and in the ankle, tarsal, and metatarsal joints during the previous year. He had never had rheumatism. The tip of his nose was thick and bulbous, and the integument in the malar region was thickened. There were typical parrot-beak nails, and fingers and toes were typically clubbed. There was distinct thickening of the legs below the calves, so that the ankle looked heavy and clumsy. This was more marked on the right side. This region was not tender.

Roentgen ray showed quite marked increase in the soft parts of all the fingers, most noticeable at the tips. The bony parts showed a marked cauliflower appearance at the tips of the end phalanges, with marked broadening of the basal portions, due to point-like projections. The forearms and arms were negative. The fifth metatarsal bones showed a thin layer of periosteal new bone, lining the shaft at the internal aspect and being quite well differentiated from the bone proper. Both fibulae and tibiae showed a very dense and quite thick layer of new bone lining both lateral aspects and extending upward above the malleoli about 6 cm. The lower thirds of the tibiae showed a marked lack of differentiation between cortical and medullary layer of bone. This layer of new bone formation was at its widest part about 0.5 cm. in thickness, and in some places not differentiated from the bone proper, which gave the lower ends of fibulae and tibiae a clumsy and misshapened appearance. The lower half of the femora showed at the anterior aspects a fine but distinctly differentiated layer of periosteal new bone. The upper thirds of both femora show quite a thick layer of dense and well-differentiated new bone

at the lateral and external aspect. This layer was about ⅛ cm. at its widest place. The joints were free and the hips and iliac crests were negative.

Case 3 (No. 31603).—A. G., aged 25, a musician by occupation, presented a pulmonary condition dating back four years. He was in the third stage of pulmonary tuberculosis, usually afebrile. The sputum was positive. He had never had pain in any of the joints, and had never noticed the clubbing of the fingers and curving of the nails. There was present clubbing of the fingers and toes, with curving of the nails of both.

The Roentgen-ray examination revealed marked increase in the soft tissues of the end phalanges of the hands, with a point-like projection at the bases. Most of the middle and distal phalanges showed marked broadening of the bases. Most of the hand bones showed advanced irregular atrophy. The left ulna showed at its lower end, extending just above the styloid process upward about 3 cm., a thin layer of new bone formation with a sharp line of demarcation. The upper arms and shoulders were negative. The fifth metatarsal bones were lined at the internal aspect with a distinct layer of new bone for-

TABLE 3 (Group 3).—Ten Patients with Clubbed Fingers and Changes in the Long Bones

Name	Age, Yr.	Years Ill	Stage	Fever	Dyspnea	Toxemia	Cough	Expectoration
L. C.	39	11	3	0	0	0	Moderate	Moderate
S. S.	43	4	3	Slight at times	0	0	Moderate	Moderate
I. G.	38	4	3	Slight	Slight	+	Severe	Profuse
A. G.	25	4	3	Slight at times	0	Slight	Moderate	Moderate
L. R.	52*	2	3	At times	At times	Slight	Severe	Profuse
H. S.	38	7	3	0	0	0	Moderate	Moderate
N. C.	35	4*	3	+	+	+	Moderate	Moderate
I. A.	35	5*	3	+	Slight	Moderate	Severe	Profuse
J. M.	36	3*	3	Occasional	Slight on exertion	Moderate	Severe	Profuse
S. A.	32	5*	3	+	Slight	Moderate	Severe	Profuse

* Period of illness expressed in months.

mation about 0.2 cm. at its widest. There was marked increase in the soft tissues of all the toes. The lower end of tibia and fibula showed at their lateral aspect, beginning just above the malleoli line and extending upward about 4 cm., a more or less fine layer of new bone, merging gradually into the normal cortical layer, showing quite a distinct line of demarcation. The upper third of the fibula is lined with quite a thick layer of periosteal new bone about 0.25 cm. in thickness, in some places showing a demarcation line, in others merging with the cortical layer of the fibula. The femora and pelvic bones were negative.

Case 4.—H. S., a Roumanian, aged 38 years, presented a lung condition which dated back seven years. He was in the second stage of pulmonary tuberculosis, running an afebrile course. The sputum was positive. There is well-marked clubbing of the fingers and toes.

Roentgen-ray examination showed that the soft tissues of all the end phalanges of the hands were greatly increased. The tips showed a moderate amount of cauliflower formation. The bases and phalanges were markedly broadened, especially in the little fingers, where there are quite marked point-like bony excrescences. The middle phalanges of almost all the fingers appear abnormally short and their bases distinctly widened. The forearms were

negative, except for a slight irregularity at the lateral aspect of the right radius just above the styloid process. The right radius presented at the aspect of its lower end, beginning one-half inch above the styloid process and extending about 2 inches, an irregularly outlined, thin fine layer of new bone. The feet were negative. The legs were negative, except for a moderate amount of irregularity of outlines in the fibula just above the lower tibiofibular joints to the extent of about 2 cm. The knees showed slight arthritic changes at the patella. The femora and pelvic bones were negative.

CASE 5 (No. 31985).—N. C., aged 35 years, a painter by occupation, showed a pulmonary condition dating back four months. He was in the third stage of pulmonary tuberculosis, running a febrile course. Sputum positive. He had never had pain in any of the joints; he had noticed enlargement of the fingers and curving of the nails for about one year. There was marked clubbing of the fingers and curving of nails, also slight enlargement of all the toes and curving of the toe nails. The lower ends of the tibiae are thickened but not tender. The patient died Nov. 11, 1915.

Roentgen-ray examination showed a very marked increase in the soft tissues of all the end phalanges. The tips of the bony end phalanges presented a distinct cauliflower formation and the bases were quite markedly widened, due to a little bony projection. The middle phalanges appeared unusually short and their bases were broadened. The rest of the bones of the hands appeared normal. The ulnae showed at their external aspects a fine layer of periosteal new bone formation extending from the styloid process upward about 3 cm. Practically the same change was seen at the external aspects of the radii. These radial and ulnar changes were symmetrical. The upper arms were negative. In the feet there was an apparent increase of soft tissues in the end phalanges, with burr-like bony outgrowths at the tips. The fifth metatarsal bone shows along its inner aspect a thin layer of periosteal new bone formation about 0.2 cm. at its widest, and presenting a sharp line of demarcation. Roentgenograms taken in various positions show that the lower thirds of tibiae and fibulae were covered with a layer of new bone formation about 0.25 cm. at its widest, and showing everywhere a sharp line of demarcation. Higher up this new-formed bone merges gradually with the normal cortex. The changes in the fibulae extend a little farther upward than in the tibiae. The contiguous portion of the tibia and fibula at the lower tibiofibular joint showed marked irregularity in outlines. The upper thirds of the fibulae, beginning just below the upper tibiofibular joint, showed a distinct thin layer of a newly formed bone at its anterior aspect. Both femora showed symmetrical changes consisting of a layer of periosteal bone at both lateral aspects, beginning just above the condyles and extending upward on the external side about 5 cm. and the internal side about 3 cm. The middle thirds of both femora show an irregularly outlined layer of new bone at both lateral aspects, about 0.5 cm. in thickness. The hips and pelvic bones were negative.

CASE 6 (No. 30529).—I. A., aged 35 years, gave a pulmonary history dating back five years. He was in the third stage of pulmonary tuberculosis, which was running a febrile course. The sputum was positive. He had never had pains in any of the joints, nor had he noticed clubbing of the fingers or curving of the nails. The nails were distinctly parrot beak in shape, thickened, cyanotic, and showed longitudinal striations. The finger tips were somewhat clubbed; there was enlargement of the lower radius and ulna, and this region was distinctly tender. The changes in the lower extremities were similar to, but less marked than those in the upper. Over the thickened area, at the lower end of the tibia and fibula, tenderness was present. The subcutaneous tissue in the malar region was also thickened.

The Roentgen-ray examination showed that there was a slight increase in the soft tissues of all the fingers, most marked at the tips and around all the interphalangeal joints. Cauliflower formation was marked only at the tips of

the end phalanges of the index and little fingers. The forearms were negative. The soft tissues of all the toes were increased and the tips of the end phalanges of the big toes showed an exaggeration of a burr-like formation. The fifth metatarsal bones appeared at the inner aspect to be lined with a thin layer of new bone perfectly regular in outline and showing a sharp and distinct differentiation between it and the cortical layer. Both tibiae show on their external aspect, beginning just above the malleolus, and extending upward about 3.5 cm., a lining of a distinct, although very thin, layer of new bone formation, with complete differentiation. The same changes were found at the posterior aspect of the lower end of the tibia. At the anterior aspect there was a very fine layer of a just beginning new bone formation extending to 3.5 cm. The femora, hips and pelvis were negative.

CASE 7.—J. M., a Hungarian, aged 36 years, a tailor by occupation, showed a pulmonary condition which dated back three years. He was in the second stage of pulmonary tuberculosis, which was running an afebrile course. The sputum was positive. He had never noticed any changes in his fingers or toes, nor had he complained of pain in the joints or bones. There was present marked clubbing of the fingers and toes, also curving and thickening of the nails. The wrist and ankle joints appeared larger than one would expect in proportion to the remainder of his skeleton. The subcutaneous tissue in the malar region was thickened and the nasal tip was voluminous.

Roentgen-ray examination revealed great increase in the soft tissues of all the fingers, most marked at the tips. Very marked bony projections at the base of the end phalanges, with marked cauliflower formation at the tips. All the phalangeal bones had an abnormally short and thick appearance, the bases being greatly broadened. The forearms and arms were negative. There was marked increase in the soft tissues of all the toes and the burr-like formation at the tips of the end phalanges was quite exaggerated. The lower ends of the tibiae showed a dense layer of new bone formation extending above the malleolus upward about 5 cm., presenting in some spots a line of demarcation, in others merging with the normal cortical layer and giving the lower end of the tibia a clumsy and misshapen appearance. The fibulae failed to show any abnormality. The rest of the bones of the lower extremities were not examined.

CASE 8.—S. A., a Russian, aged 34 years, presented a condition which dated back five years. He was in the third stage of pulmonary tuberculosis. The urine was negative, the sputum positive. The patient claimed that six years before he had rheumatic pains in his arms. Four years before he noticed the changes in the ends of his fingers and toes. The fingers and toes showed marked clubbing, also curving of the nails. The nails showed striae and the matrices were thickened. There was no tenderness over any of the long bones or joints. The long bones did not show any changes. The nose was bulbous and there was a slight thickening of the subcutaneous tissue of the malar region.

The Roentgen-ray exmaination showed that the soft tissues of all the end phalanges were greatly increased. The basal portions of the end phalanges were broadened and showed lateral excrescences, most marked in the little fingers. The tips of the distal phalanges showed a moderate amount of burr-like projections. The rest of the bones of the hands failed to show any abnormality. The lower end of the ulna showed a thin layer of periosteal new bone, beginning just above the styloid process and extending upward about 2.5 cm., gradually merging into the normal cortex. No abnormalities were seen in the upper arms. The soft tissues of all the toes were greatly increased. The tips of the distal phalanges showed moderate cauliflower formation. Otherwise no abnormalities were seen in these bones. At the internal aspect of both tibiae there was a layer of new bone formation, beginning just above the internal malleolus and extending upward, about 10 cm. in diameter at its widest.

The external aspect of the tibia and the internal aspect of the fibula from the lower tibiofibular joint upward about 2 cm. showed marked irregularities

in outline, with many bony projections. Practically the same condition was seen on the lateral plate at the anterior and posterior regions. The anterior aspects of the femora showed a dense layer of a new bone formation about 0.5 cm. at its widest point, and extending upward about 15 cm., gradually merging into the normal cortex. There was a free space between this new bone formation and the cortex. No abnormalities were seen in the pelvic bones.

Case 9 (No. 30729).—L. R., a Russian, aged 38 years, showed a lung condition which dated back three years. He was examined Nov. 26, 1915, and found to be in the third stage of pulmonary tuberculosis. The sputum was positive. The course of the disease was afebrile for most part, with slight variations. There was thickening of the nasal tip and of the subcutaneous tissue in the malar region. The finger nails were thickened and curved, and showed longitudinal striations. The matrices are thickened and showed slight cyanosis. There was moderate thickening of the soft tissues of the finger tips. The lower part of the forearms, in the region of the wrist, was thickened and clumsy in appearance, and this area was distinctly tender. Similar changes were not present in the legs, but the toes showed changes similar to the fingers.

Roentgen-ray examination revealed a great increase in the soft tissues of all the end phalanges and burr-like excrescences at the tips, with marked broadening of the bases of the end and middle phalanges. The outer aspect of the first metacarpal bone showed a distinct irregularity along its middle third, due to an irregularly outlined layer of periosteal new bone formation. The entire metacarpal bone appeared clumsy and considerably broadened. The lower ends of the ulna showed just above the styloid process a fine layer of new bone formation, with a distinct line of demarcation extending upward for about 4 cm. Roentgenograms made in various positions showed that the same changes were present at the dorsal aspect of the ulnae. The right radius showed a slight irregularity in the outlines just above the styloid process, extending upward about 2 cm. The upper arms were negative. There was marked cauliflower formation at the tips of the end phalanges of the toes. The fifth metatarsal bone presented at both its lateral aspects a thin layer of new bone formation, showing in some places a distinct line of demarcation. This line of demarcation disappeared entirely at the middle portions, where the entire bone showed a lack of differentiation between cortex and medulla, the latter appearing just as dense as the former. The lower ends of the tibiae just above the malleolus and extending upward about 4 cm. showed at the anterior, posterior and external aspects a layer of new bone formation with a sharp line of demarcation and varying in thickness from ¼ to ⅓ cm., and extending upward about 4 cm. The fibulae did not show any changes. The femora and pelvic bones were negative.

Case 10.—I. G., aged 38, a hatmaker by trade, presented an illness dating back four years. He was in the third stage of pulmonary tuberculosis, running an afebrile course. The sputum was positive. He had marked clubbing of the distal ends of the fingers and toes, with great curving of the nails. He had never had pain in any joints of the body. His nose was markedly globular, and there was a thickening of subcutaneous tissues in the malar region. The patient died Oct. 29, 1915.

The Roentgen-ray examination showed that there is marked increase in the soft tissues of all the finger tips, a moderate amount of cauliflower formation at the tips of the distal phalanges, and a quite marked broadening of the bases of the same phalanges, due to point-like excrescences most marked in the little fingers. The middle phalanges appear somewhat shortened and widened at the basal portions. There was some roentgenologic evidence of rarefaction in the upper three quarters of both ulnae and at the upper halves of the radii). In the middle portions of the ulnae there was marked decrease in the differentiation between the cortex and medulla. The upper arms were nega-

tive. There was slight irregular thickening of the cortex at the lateral and outer aspect of the middle portion of the fifth metatarsal bone on the right side and to a much lesser degree on that of the left side. There was a point-like exostosis at the lateral and outer aspect of the head of the first metatarsal bone on the right side. The rest of the bones and joints of the feet were negative. There was a layer of new bone at the lateral and inner aspect of both tibiae, beginning just above the malleoli and extending upward 5 cm. There was marked irregularity at the lateral aspects of both tibiae and fibulae along the tibiofibular joint, extending upward about 3 cm., especially along the tibiae. There was evidence of moderate amount of rarefaction in the middle and upper portion of the right fibula.

The pathologic report gave an anatomic diagnosis of chronic ulcerative pulmonary tuberculosis, tuberculosis laryngitis and tracheitis with ulceration, tuberculous ulcer of the rectum, miliary tubercles of the lungs, chronic adhesive pleuritis, ossified periostitis, chronic adhesive pericarditis, atheromatous change in pulmonary arteries, dilatation and hypertrophy of right auricle and ventricle, edema of the skin and mesentery, ascites, bilateral hydrothorax, chronic passive congestion of the liver, thrombosis of left suprarenal vein and of a branch of the left pulmonary artery.

Microscopically a section of the various bones (fibula, tibia, radius, ulna, fifth metatarsal, terminal phalanx, middle finger, in the areas corresponding to Roentgen-ray changes) revealed a constant abnormality. There were masses of new bone within the periosteum, separating it from the old bone. This new bone was irregular in distribution and was composed of numerous osteoblasts imbedded in a homogeneous matrix, similar to the old bone in general, but not so prominently laminated. The bone marrow was fatty; the process was best seen in the lower end of the radius and tibia. A section of the lower end of the radius showed the periosteum invaded by irregular masses of new bone. This new bone was irregular in distribution and was composed of numerous osteoblasts embedded in a homogeneous matrix similar to the old bone. It likewise showed lamination, not, however, as prominently as the older bone. This ossifying process was seen in all portions of the periosteum in the section. At the lower end of the tibia the periosteum everywhere showed a similar ossifying process to that described above.

I wish to express my thanks and appreciation to Dr. Scholz of the Roentgen-ray Department at Montefiore Hospital for his careful work done in this connection.

TYPHOIDIN QUOTIENTS

AN ANALYSIS OF THE FACTORS OF UNCERTAINTY IN THE CUTANEOUS TYPHOIDIN TEST *

EUGENE S. KILGORE
SAN FRANCISCO

In connection with a recent study[1] of the cutaneous typhoidin test, which was introduced by Gay and Force[2] as an index of typhoid immunity, an objective method of reading such cutaneous diagnostic reactions was described. Instead of reporting the test as positive, negative or doubtful, from the general appearance of the inoculated spots, the diameters of the areolae are measured with a suitable millimeter gage, preferably one which can be set to the diameter to be measured without exhibiting the reading until afterward. The result of a test is recorded as the quotient of the diameter of the test areola divided by that of the control. The advantages of this procedure are, first, that after adjusting the gage to the diameters of the areolae, the bias of the observer can be entirely eliminated in expressing the results of the test, and, second, that the quotients so obtained lend themselves readily to quantitative analyses according to the statistical theory of variables. Reasons were given for using the quotient rather than the difference between the two diameters. It is recognized, of course, that other characters, such as swelling, induration and depth of color, may contribute to the formation of judgments concerning such diagnostic skin reactions. As a rule, however, these characters vary with the diameters; and for statistical investigations, it is felt that the advantages of the definite and uniform system of measurements possible for the diameters outweigh any objections to the ignoring of other qualities of the reactions.

It was found that with the dry preparation of typhoidin used there were average differences between groups of typhoid immunes and nonimmunes, but that the differences were small in comparison with the variation among individuals in the same group, so that the test had little value for the individual case. The desirability, therefore, became apparent of examining possible sources of variability in

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* Submitted for publication Aug. 9, 1916.

* From the Department of Medicine of the University of California Medical School.

1. Kilgore, E. S.: The Typhoidin Quotient, THE ARCHIVES INT. MED., 1916, **17**, 25.

2. Gay, Frederick P., and Force, John N.: A Skin Reaction Indicative of Immunity Against Typhoid Fever, THE ARCHIVES INT. MED., 1914, **13**, 471.

the results of the test other than differences in typhoid immunity. Also, the dry typhoidin had been substituted for the aqueous solution previously used, because it was thought that the latter deteriorated rapidly.[3] The question now should be answered whether or not the dry powder, possibly because it is slightly hygroscopic, loses potency on standing.

In order to determine the sources of variability of the test other than differences in immunity, the personal equation in making the measurements has been investigated, as well as variations in other factors, such as the mechanical trauma and the amount of the applications absorbed. In order to test the keeping qualities of the dry typhoidin an old preparation of it has been compared with a new preparation on a new series of cases. At the same time advantage was taken of the opportunity to compare several different preparations of typhoidin.

The technic was the ordinary Pirquet technic heretofore described.[1]

SOURCES OF ERROR IN THE APPLICATION AND READING OF THE TYPHOIDIN CUTANEOUS TEST

The Personal Equation of the Observer in Measuring the Areolae.—In order to determine the variation to be expected among these cutaneous reaction determinations on account of the personal factor of the observers alone, a pair of one-day old areolae (one spot inoculated with "T_4 (new)" and the other with the corresponding control powder, described later, were measured successively forty-one times by as many different persons (twenty-nine physicians and twelve medical students) in the University Hospital, all the measurements being made in one forenoon and under the same conditions of light as nearly as possible. The subjects of the experiment used a pair of draftsman's compasses and the measurements therefrom were then transferred to a millimeter scale. Possibly on account of the exposure of the arm, during the first few measurements both areolae seemed to increase somewhat in diameter, according to both my own measurements and those of the others. The measurements of the first six subjects were therefore thrown out, and the results of thirty-five only are included in Table 1.

Although each person was instructed to set the calipers to the extreme limits of the areolae which he could see, it is apparent from the table that there was great variation among the measurements by different ones; and this is inevitable from the fact that these areolae are not sharply limited at the periphery, but fade gradually. The

3. Gay, Frederick P., and Claypole, Edith J.: An Experimental Study of Methods of Prophylactic Immunization Against Typhoid Fever, THE ARCHIVES INT. MED., 1914, **14**, 671.

TABLE 1.—MEASUREMENTS OF ONE PAIR OF AREOLAE BY THIRTY-FIVE PERSONS DURING ONE FORENOON

	Mean	Probable* Error	Lowest	Highest	Theoretical Limits*
Test spot	21.2 mm.	±2.64 mm.	14.8 mm.	29.4 mm.	10.91 to 31.49 mm.
Control	6.52 mm.	±0.85 mm.	4.2 mm.	9.2 mm.	2.76 to 10.28 mm.
Typhoidin quotient	3.31	±0.4	2.45	5	1.51 to 5.11

* The probable error was obtained according to the formula,

$$E = \pm 0.6745 \times \text{the standard deviation}$$

(Davenport: "Statistical Methods with Special Reference to Biological Variations," John Wiley and Sons, New York, 1914). A probable error of ±2.64 mm. for measurements of the test spot means that if one of the readings in the series is picked out at random, the chances are even that it will differ by more or by less than this amount from the mean.

The standard deviation of the test spot measurements is 3.76 mm. according to the formula:

$$\text{Standard deviation} = \sqrt{\frac{\text{Sum of the squares of all deviations from the mean}}{\text{Number of variates}}}$$

It is an interesting fact that in a frequency distribution of the symmetrical or nearly symmetrical type, a range of six times the standard deviation includes about 99 to 100 per cent. of all the values (G. U. Yule: "Introduction to the Theory of Statistics," Charles Griffin & Co., London). That is, in the present case, assuming the distribution to be symmetrical, three times the standard deviation subtracted from the average ($21.20 - 3 \times 3.76 = 10.91$) would represent approximately the lower limit, and the same amount added to the average ($21.20 + 3 \times 3.76 = 31.49$), approximately the upper limit of measurements of these areolae if the series were extended to include observations by many more persons of the same general character as these thirty-five. The distribution in all these cases, however, is more or less askew, and the series so small that these theoretical limits are quite rough. It will be seen, however, that they are not very far from the actual highest and lowest figures recorded.

greatest disagreement (largest probable error) is seen in the measurements of the typhoidin areola. One man will detect a faint blush 29 mm. in diameter, while another sees about half as much. Fortunately, the one who makes the small measurement of the test spot also, as a rule, makes a conservative determination of the control areola, so that the quotients show proportionately less variation than either the dividends or divisors, a fact which emphasizes the utility of control inoculations in such tests.

It should be stated here, however, that while the test areola in this case was judged to be rather more ambiguous than the average, it was less so than some; so that the comparison between control and test spot is not always so effective in limiting the personal equation as is shown in these figures. In typhoidin, tuberculin and other similar cutaneous tests there is at times a quite distinct small, fairly sharply limited areola, surrounded by a much wider but faint and gradually fading blush. The control spot may have the same double character, but as a rule in such cases it is of the ordinary type. If such a pair of areolae were submitted to different observers for measurement, the resulting quotients would certainly be more at variance than is the case in this series. In order to be consistent throughout it is our prac-

tice always to measure the diameter of the outermost blush that can be seen. But in so doing it is recognized that the measurements probably do not always represent corresponding degrees of the same biologic process. For all gradations of the double areola described above are encountered, from the well-marked outer blush to one which is scarcely visible; and there is no doubt that among the cases in which but one areola is observed are some which correspond to the inner brighter areola of the double type. That is, it may well be that the faint outer blush is really present, but is concealed in these cases by the heavier epidermis, or that it involves a deeper set of capillaries so that it escapes observation and measurement. It is also true, however, that the cases with the double areola, and hence with the high typhoidin quotients, are the ones which all would agree showed a very "strong reaction."

In the investigation of a series of cases (to which, as has already been intimated, the use of the test should be confined) it is reasonable to expect that if the measurements were all made by one observer they would be more consistent. To determine the variation among my own readings I measured during the same forenoon the same two areolae described above once for each measurement by the other observers. Omitting, as before, the first six figures, the results for the last thirty-five are shown in Table 2.

TABLE 2.—MEASUREMENTS OF ONE PAIR OF AREOLAE THIRTY-FIVE TIMES BY ONE PERSON DURING ONE FORENOON

	Mean	Probable Error	Lowest	Highest	Theoretical Limits
Test spot	21.9 mm.	±1.07 mm.	19 mm.	25.2 mm.	17.2 to 26.7 mm.
Control	6.08 mm.	±0.42 mm.	5 mm.	7.5 mm.	4.2 to 7.9 mm.
Typhoidin quotient	3.65	±0.28	3	4.82	2.4 to 4.9

The probable errors, which may be taken as measures of the inconsistency in these readings, are about half as great in Table 2 as in Table 1. *In other words, about half the uncertainty connected with these measurements is due to differences in the separate standards of observers, and can be eliminated in a series of observations if they are all made by one worker.*

That the discrepancy among these measurements is largely due to causes which vary from hour to hour is shown by the considerably better results when I measured a similar pair of areolae an equal number of times but in quick succession during a half hour. These results are shown in Table 3.

TABLE 3.—Measurements of One Pair of Areolae Thirty-Five Times by One Person During a Half Hour

	Mean	Probable Error	Lowest	Highest	Theoretical Limits
Test spot	16.5 mm.	±0.7 mm.	13.3 mm.	18.5 mm.	13.1 to 19.9 mm.
Control	4.6 mm.	±0.15 mm.	4.1 mm.	5 mm.	3.9 to 5.3 mm.
Typhoidin quotient	3.6	±0.19	3.12	4.28	2.75 to 4.46

Although the areolae in this case resembled in every way the ones in the previous experiment, it will be noted that the probable errors are only about one third to two thirds as large as before. The differences between Tables 2 and 3 are important in connection with the interpretation of cutaneous reactions; and the larger discrepancies of Table 2 are of course the ones which correspond more closely to the conditions of actual practice in gathering statistics from a series of cases. *That is, the results of reading these cutaneous tests depends considerably on some such conditions as the hour of the day, perhaps the atmospheric temperature, and the activity of the subject, as well as possibly on unavoidable variation in the way in which the observer exercises his faculties.*

Variations in the Typhoidin Cutaneous Reaction which are Independent of Allergic Differences.—After allowing for inaccuracies in the readings, it is certain that not all of the variations in the size of these inoculation areolae are due to allergic mechanisms of any sort. Variations in the strain of the organism used, materials in the culture mediums, methods of preparation, etc., may affect the results, as will be shown later. But in addition to these variables, which can be standardized for a given series of observations, there are others inherent in the method. Thus, the amount of typhoidin powder used in each test, even if it could be accurately measured, is no indication of the amount absorbed. In nearby areas the skin may vary in glandular content, hair follicles or otherwise; but perhaps the most variable factor present is the amount of trauma inflicted by the chisel, even when the greatest care is taken to standardize the technic.

To test the effect of these variables, Dr. E. H. Falconer was good enough to make 100 circular abrasions on the front of my thigh, by rotating a chisel with a 2.5 mm. blade. His aim was to make them all as nearly as possibe alike and just deep enough not to cause bleeding. Half of them were then inoculated with typhoidin powder "T_4 (new)" (described later), the other half were left to show the effect of the mechanical trauma alone. On the following day I measured the transverse diameters of all the 100 areolae, using the technic already described to avoid being biased by seeing the measurements during the act of taking them. In the order in which the abrasions were made the

areolae were divided into pairs, one test spot and one control, for the purpose of forming typhoidin quotients.

On inspection of both the control and the inoculated spots a certain amount of variation was very evident, which is reflected in the results of the measurements shown in Table 4.

TABLE 4.—MEASUREMENTS OF FIFTY PAIRS OF AREOLAE ON ONE SUBJECT MADE BY ONE OBSERVER DURING ONE-HALF HOUR

	Mean	Probable Error	Lowest	Highest	Theoretical Limits
Control	4.97 mm.	0.26 mm.	3.7 mm.	6.3 mm.	3.29 to 6.65 mm.
Typhoidin	10.16 mm.	0.87 mm.	7 mm.	12.6 mm.	6.51 to 14.01 mm.
Quotient	2.07	0.24	1.25	2.73	1.03 to 3.11
Possible quotient*	.....	.....	1.11	3.4	

* Obtained respectively by dividing the greatest test spot diameter by the smallest control and vice versa.

As these measurements were made in quick succession, they are to be compared with Table 3 to show the added influence of variations connected with the application of the test. The fact that the greatest difference between the probable errors in the two tables happens in the case of the uninoculated control spots suggests that much of the variation comes through the inability of the operator always to produce the same amount of trauma. It should be stated, however, that the control abrasions were made before those intended for inoculation, so that there was opportunity for the operator to better the standardization of his technic by the time he made the second fifty abrasions.

PREPARATIONS OF TYPHOIDIN POWDER

In order to test the keeping qualities of typhoidin powder and also to compare several preparations of typhoidin, a new series of tests was undertaken on 103 students, nurses, physicians and others connected with the University of California Hospital and the Hooper Foundation for Medical Research. By using the ordinary Pirquet technic as before, nine circular abrasions were made on the arm of each subject, making them all as nearly as possible equal in depth (just short of bleeding) and on skin of as nearly as possible the same texture. One spot was not inoculated, and was for the purpose of showing the effects of the mechanical trauma alone. On each of the other eight spots was rubbed a little of one of the following preparations:

1. "T_2 (old)": This typhoidin was described in a former communication.[1] It was prepared about eighteen or twenty months previously in the department of pathology and bacteriology of the University of California, and had been kept meantime in a rubber-corked, amber-colored bottle in the open laboratory.

2. "C_2 (old)": This was the control application, the manufacture, preservation and use of which were the same as for "T_2 (old)."

The other preparations, which follow, were kindly furnished by Dr. Karl Meyer of the George Williams Hooper Foundation for Medical Research of the University of California. Their manufacture was completed only a few hours before beginning these experiments, and they were kept in amber-colored bottles in a desiccator. A detailed description of methods of preparation is to be given in a forthcoming article by Dr. Meyer, and the following statements will suffice here:

3. "T_4 (new)": This was prepared from the same strain (Dorset) and in the same way (using Witte's peptone) as "T_2 (old)."

4. "C_4": This was the corresponding control powder.

5. "T_7": This powder was prepared from eight strains, known as "Sch., B., L., Kuhn, 66, 94, 38 and M." Liverbroth and Witte's peptone were used. Hence "C_4" also serves as control for this typhoidin.

6. "T_3": This powder was prepared from Rawlings strain of *Bacillus typhosus,* using Chapoteaut-Paris peptone.

7. "C_3": This was the corresponding control powder.

8. "T_2": This was the Dorset strain of *B. typhosus.* Chapoteaut peptone was used, so that the corresponding control powder is "C_2."

About twenty-four hours after inoculation the diameters of all the areolae were measured in a direction across the arm. A summary of the results is expressed in Table 5. The measurements of the uninoculated spots are in millimeters. In order to show the relative amount of added reaction about the spots which were inoculated with the control powders, the diameter of each was divided by that of the uninoculated spot and these quotients are shown in the tables: The typhoidin inoculated abrasions, on the other hand, are to be interpreted according as they exceed the reactions about the spots inoculated with the corresponding control powders; and they are, therefore, tabulated as the quotients of the test spot diameter divided by the control spot diameter, that is, as "typhoidin quotients." In each case the first figure given is the mean for the corresponding group, and the "plus or minus" figure below it is the probable error of the mean.[4]

4. This was obtained (Davenport, Footnote to Table 1) according to the formula:

$$\text{Probable error of the mean} = \pm 0.6745 \sqrt{\frac{S}{n^2}}$$

In the larger groups, like the group of immunes, which is composed of the subgroups A, B and C, the probable errors were first computed for the subgroups; and from these figures (that is, by adding the S's and the n's) the probable errors for the composite groups were estimated. Since the averages for the subgroups were not quite identical, the probable errors of the large groups computed in this way may not be quite the same as if an entire, new calculation had been undertaken in each case. It is certain, however, that whatever inaccuracies may be present from this cause are small in comparison with the probable inaccuracies of the probable errors themselves, and are therefore inconsequential.

TABLE 5.—Results of Typhoidin Tests on a Series of Cases

Group	Classification of Subjects	Uninoculated Areola, Mm.	Control Inoculations			Typhoidin Quotient					Aver. T
			C_2 (old)	C_4 (new)	C_5	T_2 (old)	T_4 (new)	T_7	T_3	T_5	
A	17 who gave history of typhoid fever	4.2 ±0.11	1.33 ±0.09	1.18 ±0.04	1.45 ±0.09	1.53 ±0.07	1.65 ±0.07	1.28 ±0.06	1.44 ±0.07	1.6 ±0.06	1.5 ±0.04
B	22 who had had army vaccine	3.99 ±0.07	1.25 ±0.06	1.13 ±0.04	1.23 ±0.06	1.38 ±0.06	1.51 ±0.04	1.35 ±0.04	1.42 ±0.05	1.42 ±0.04	1.41 ±0.06
C	38 who had had sensitized vaccine	4.11 ±0.06	1.19 ±0.02	1.1 ±0.02	1.2 ±0.02	1.51 ±0.05	1.57 ±0.04	1.28 ±0.04	1.4 ±0.04	1.6 ±0.04	1.47 ±0.03
D	75 who had had typhoid* or vaccine* of either kind	4.1 ±0.05	1.18 ±0.02	1.07 ±0.01	1.2 ±0.02	1.51 ±0.03	1.6 ±0.02	1.33 ±0.02	1.45 ±0.03	1.57 ±0.03	1.46 ±0.01
E	22 who had had neither typhoid nor vaccine	3.81 ±0.07	1.22 ±0.05	1.17 ±0.03	1.26 ±0.05	1.42 ±0.05	1.45 ±0.05	1.3 ±0.04	1.41 ±0.05	1.48 ±0.02	1.41 ±0.04
F	32 who had had but one course of immunization	4.2 ±0.05	1.16 ±0.02	1.12 ±0.03	1.17 ±0.03	1.39 ±0.03	1.51 ±0.04	1.31 ±0.03	1.4 ±0.05	1.52 ±0.05	1.42 ±0.03
G	29 who had had more than one course of immunization	3.9 ±0.06	1.26 ±0.03	1.11 ±0.02	1.25 ±0.02	1.55 ±0.06	1.58 ±0.04	1.31 ±0.04	1.42 ±0.04	1.53 ±0.04	1.43 ±0.03
H	General averages for all subjects	3.88 ±0.04	1.2 ±0.02	1.09 ±0.02	1.21 ±0.02	1.49 ±0.03	1.57 ±0.02	1.33 ±0.03	1.44 ±0.03	1.55 ±0.03	1.45 ±0.02

* History of typhoid fever at any time or antityphoid vaccination within the preceding ten months.

The first column in Table 5 shows the averages of measurements of the uninoculated spots. The lowest average, 3.81 mm., is in the group with negative history, the highest, 4.2 mm., is in the group of those who had had one course of typhoid immunization and also in the typhoid group. The suggestion from these averages is that those who have had typhoid fever or one course of vaccination tend to react more than others to mechanical trauma of the skin. Such a conclusion should never be drawn from averages, however, without first taking into consideration the number of the variables from which the averages are drawn and the amount of variation among them, and accordingly the possibility that the differences observed between the averages may be the result merely of "fluctuations of sampling." The amount of variation (relative to the number of observations) among the variables

underlying these two averages is reflected in their probable errors, 0.11 and 0.07 mm. According to the formula,

$$\text{Probable difference of } A_1 \text{ and } A_2 = \sqrt{E_1^2 + E_2^2}$$

the probable difference between these two averages is

$$\sqrt{0.11^2 + 0.07^2} = 0.13 \text{ mm.}^5$$

This means that if there is really no difference between these two classes of persons in their tendency to react to mechanical trauma, then if the work were repeated on equal numbers of similar cases, the chances would be equal that the differences between the two averages would be greater or less than 0.13 mm. The actual difference between the two averages here considered is 0.39 mm., or three times the probable difference. It can be shown[6] that there is about one chance in twenty-one that two averages as far apart as these have been derived from the same kind of material, that is, that the differences are due to errors of sampling alone. This would lend a very fair degree of probability to the idea that a real difference in the tendency to react to cutaneous trauma exists between those who have had typhoid fever and those who have not, if it were not for the fact that the two averages 4.2 and 3.81 were selected for comparison because they are respectively the highest and the lowest among the seven figures under consideration. A simple calculation shows that if two out of these seven averages were picked without selection there is exactly one chance in twenty-one that these particular two averages would have been taken. The conclusion, therefore, is that the difference between these averages is exactly what should be expected to result solely from the variability in the material; in fact, they are nearer the variations theoretically to be expected from "errors of sampling" than one would have any right to anticipate.

There is, of course, no reason to expect that one class of these subjects would react more to simple trauma than another class; and these average reactions have been dwelt on because they illustrate so well the mistakes frequently made, particularly in medical literature, in interpreting averages. Differences which superficially seem very striking and significant may often, as in this case, be shown to be entirely devoid of meaning, if the trouble is taken to examine in the manner here illustrated the material from which they are derived.

As might be expected, similar calculations show that among the reactions to the various control powders the differences between the

5. "The probable difference between two averages, A_1 and A_2, of which the probable errors E_1 and E_2 are known, is the square root of the sum of the squared probable errors" (Davenport, Footnote to Table 1).

6. Davenport, Footnote to Table 1.

averages for different groups of individuals, though at first suggestive of differences between the groups, are not large enough in relation to their probable errors to be at all significant. Some of the greatest differences, moreover, are between groups D and E; and, since these average quotients depend on the measurements of the uninoculated spots, which formed the divisors, the average difference between these measurements in these two groups practically accounts for the differences between the quotients. The general averages for all groups (*H*) show only minor differences between the control powders, which are easily chargeable to fluctuations of sampling.

Unfortunately for the usefulness of the typhoidin test, the typhoidin quotients (last five columns of Table 5) show no greater relative group differences than the control reactions or the uninoculated spots. It would have to be admitted, therefore, that these results were well within the limits of experimental error and might be entirely without significance of typhoid immunity if it were not for the fact that the results with the different preparations agree among themselves and with those of a previous series[1] as well as with the observations of other observers.[2] A further suggestion that the typhoidin test bears some relation to typhoid immunity is found in a comparison of groups F and G. Those who have had two or more courses of typhoid immunization show slightly higher quotients than those who have had but one course; and this is true with all the preparations of typhoidin except "T_7." in which case the two averages are equal.

The different preparations of typhoidin show only minor differences in the results. The old preparation, "T_2 (old)," shows slightly but only slightly less contrast between the groups of immunes and nonimmunes than the corresponding "T_4 (new)," which was freshly prepared; and the general average in all classes was a little greater with the new preparation. If these averages were based on thousands of observations instead of on one hundred, they would undoubtedly indicate that over a period of two years the dried typhoidin loses a small part of a weak ability it had at the outset to call forth a specific reaction, and that it also loses some of its original nonspecific toxicity. The figures as they stand, showing small contrasts in proportion to their probable errors, can only be interpreted as suggesting that typhoidin undergoes these changes with age. It can be said quite definitely, however, that the changes with age are not great.

As to the other preparations of typhoidin which were tried, "T_7" (mixed strains, Witte's peptone), "T_3" (Rawlings' strain, Chapoteaut peptone), "T_2" (Dorset strain, Chapoteaut peptone), it will be seen by comparing groups D and E and groups F and G in Table 5 that so far as these figures can be relied on, these preparations appear to be inferior to "T_4 (new)," which was prepared from Dorset strain,

Witte's peptone being used. They show less contrast between immunes and nonimmunes and between those who had had but one course of vaccination and those who had had more than one course.

The last row (H) in Table 5, which shows the general averages for all the groups, is interesting in that it exhibits independently of specific differences among the groups of individuals (which differences have been shown to play a very minor rôle in the total reaction) the approximate proportions of these cutaneous reactions which are due to individual factors. Mechanical trauma alone is accountable for an areola with average diameter of 3.88 mm., that is, 1.38 mm. in excess of the width of the chisel. The material in the control powder increases the diameter of the area of redness by from 9 to 21 per cent., and the material from the typhoid organisms, together with that from the culture mediums, produces an additional 33 to 57 per cent. increase over the control inoculation. Compared with this, 33 to 57 per cent. average difference between the control and the typhoidin spot diameters is less than 15 per cent. difference between the average typhoidin quotients of immunes and nonimmunes. *In other words, what may be termed the nonspecific toxicity of typhoidin has three or more times as much influence on the results of the reaction as any specific differences among the subjects related to their previous experience with typhoid infection or vaccination.*

This nonspecific toxicity may be due to the material of the typhoid organisms themselves or to bodies which they have split off from the proteins of the culture mediums. Whatever substances are responsible for it, it seems clear that this nonspecific toxicity, itself undoubtedly quite variable in its effects on different persons, is the thing that almost completely overshadows the specific part of the reaction and makes impossible any reliance on the test for individual cases. And until some way is found of very much reducing this disturbing element in the reaction (possibly by changes in the technic of preparation of the typhoidin or by adopting some other criterion for determining the results than the diameters of the twenty-four-hour areolae), little can be hoped from any use of the test. It must be remembered, also, that even if this alteration were accomplished, more evidence would still be needed to show that the specific reaction was definitely connected in a quantitative way with immunity to typhoid fever, and that the two things were not simply usually or occasionally associated.

INTRACUTANEOUS TYPHOIDIN TESTS

So far the intracutaneous technic has not proved itself better for typhoidin[7] than the Pirquet cutaneous method introduced by Gay and

7. Austrian and Bloomfield: THE ARCHIVES INT. MED., 1916, **17**, 663.

Force. Our own experience with it was entirely disappointing, since in a series of ninety-one cases the reactions after twenty-four hours were just as pronounced (if anything a little more so) among those with negative history as among the groups which had had typhoid fever or prophylactic inoculations. Our experiments, while not conclusive, in that only one strength of typhoidin solution was used for the injections (1 to 100 of "T_4 (new)," evidently a much too strong solution) and only the diameters of the twenty-four-hour areolae were measured, left us with the feeling that little is to be expected from typhoidin applied by any technic unless some way can be found to overcome the large nonspecific reaction which it produces. The suggestion of Pulay[8] to interpret the reactions according to their persistence rather than the diameters of the areolae should be further investigated; and work to this end is soon to be reported by Force from the department of hygiene of this university.[9]

COMMENT AND SUMMARY

The facts brought out in this study indicate even more strongly than those formerly reported[1] that the cutaneous typhoidin test should not be relied on as an index of immunity in individual cases, and that even in a study of groups of cases its results need to be considered with much conservatism. The use of "typhoidin quotients" and of statistical methods of analyzing them, while throwing light on the shortcomings of the typhoidin test, are in no way responsible for them, for although the uncertainties in measuring the areolae, which have been analyzed in this report, have been found to be very considerable, there is no reason for supposing that they are greater in any way than the uncertainties involved in simply judging the result of a skin test. After the measurements are made, the mathematical methods of dealing with them (as previously explained[1]) are practically identical with the subconscious methods involved in the formation of judgments as to the results of the test, but are of course free from all further vagaries involved in such judgments. It is again urged that similar methods of study should be applied to other cutaneous tests in order to ascertain much more definitely the amount of reliance which can be placed on them.

These studies concerning the amount of inaccuracies in reading the cutaneous typhoidin reactions may be presumed to represent very nearly the conditions which exist for other similar cutaneous diagnostic tests, and may be summarized as follows: When a single pair of areolae were measured many times in rapid succession by one individual, the resulting typhoidin quotients have a probable error of 0.19,

8. Pulay, E.: Wien. klin. Wchnschr., 1915, **28**, 1189.

9. Force, J. N., and Stevens, Ida M.: Further Studies on Typhoidin, THE ARCHIVES INT. MED., to be published.

or about 5 per cent., of the general average of the quotients. When the same measurements are made by the same individual during the course of a forenoon, changes either in the observer or in the areolae or both result in a probable error among the quotients of 0.28, or about 8 per cent. This represents most nearly the amount of variation to be expected from measurement errors in a series of cases observed by one person. If the readings of a number of observers made on one pair of areolae during one forenoon are compared, the probable deviation of the typhoidin quotients from the average of the group is 0.4, or 12 per cent. of the average. In addition to variations in measuring the areolae, other discrepancies are connected with the application of the trauma and the inoculations. A rapid series of readings by one observer of a number of tests applied on the same subject yielded a probable error of the quotients of 0.24, or about 11 per cent. of the average quotient. The difference between this result and the 5 per cent. when the same experiment was performed with one pair of areolae is 6 per cent.

In other words, each of the following factors contributes to the inaccuracies in the readings in about the proportion given:

1. Indefiniteness in areola outlines, 5 per cent.
2. Effect of scattering the readings over several hours, 3 per cent.
3. Effect of participation by many observers, 4 per cent.
4. Effect of variations in the trauma, etc., 6 per cent.

CONCLUSIONS

1. A second series of cases has emphasized the total unreliability of the cutaneous typhoidin test in its present state of development as an index of typhoid immunity in persons and the need for much caution in interpreting its results even in a considerable series of cases. The reasons for this unreliability appear to be, first, unavoidable variations in the application of the test; second, indefiniteness of the readings, and, third, and most important, the relatively large amount of nonspecific reaction which is produced by typhoidin—upward of three times the amount that can be attributed to specific differences among the subjects.

2. In varying degrees, similar sources of inaccuracy undoubtedly exist for other cutaneous tests, and should be investigated.

3. The dried typhoidin is little affected by age.

4. The typhoidin test when applied intracutaneously in a dilution of 1 to 100 and read twenty-four hours later is valueless.

A COMPARISON OF TWO METHODS OF VACCINATING AGAINST TYPHOID FEVER*

EUGENE S. KILGORE
SAN FRANCISCO

Of the fifteen or twenty recognized methods of immunizing against typhoid fever,[1] the one most commonly used in this country has been that employed in the United States Army, which consists of three injections at seven or ten day intervals, the first of 500 million and the second and third of 1 billion each of a heat-killed culture of a mild strain of typhoid bacillus. Another method which has been extensively used in California in the last three years is that introduced by Gay and Claypole.[2] This vaccine consists of alcohol-killed cultures of the typhoid organism which have previously been treated by an immune serum, a so-called sensitized vaccine. The cultures are then dried and ground, suspended in salt solution, and the sediment redried, and weighed amounts are used in immunizing. Experimentally in rabbits such a vaccine was thought to produce more permanent immunity than nonsensitized vaccine, and it was expected to give fewer unpleasant symptoms following human inoculation.

In several hundred vaccinations of university students, Force[3] was convinced that the reactions were milder than with the vaccine previously used; and our experience in the University Hospital led us to the same belief. Thus, in the summer of 1912, sixty members of the University of California Hospital staff were vaccinated according to the United States Army plan with vaccine obtained through the courtesy of the Letterman General Hospital. The next year about seventy new subjects were vaccinated with sensitized vaccine according to the three-day interval plan, the vaccine being prepared in the University of California department of pathology and bacteriology under the direction of Professor Gay. Both years the attempt was made to get

* Submitted for publication Aug. 19, 1916.

* From the Department of Medicine of the University of California Medical School.

1. Metchnikoff and Besredka: Ann. de l'Inst. Pasteur, 1911, **25**, 193. Friedberger, in Kraus and Levaditi: Handbuch der Technik und Methode der Immunitätsforschung, Fischer, 1908, **1**, 722. Fornet, in Kolle and Wassermann: Handbuch der pathologische Mikroorganismen, Ed. 2, Fischer, 1912, **3**, 837. Gay and Claypole: THE ARCHIVES INT. MED., 1914, **14**, 671.

2. Gay and Claypole: Footnote 1.

3. Force: Am. Jour. Pub. Health, 1913, **3**, 750.

reports of symptoms and temperatures following injections, and the following comparison is shown by the records:

	Army Vaccine (1912)		Sensitized Vaccine (1913)	
Local Reaction	Per Cent.	No. Reports	Per Cent.	No. Reports
Slight or zero	86.6	157	99.4	172
Moderate	9.4	17	0.6	1
Severe	4.0	7	0.0	0
	100	181	100	173
General Reaction				
Slight or zero	94.0	160	99.3	140
Severe	6.0	10	0.7	1
	100	170	100	141
Highest Temperature				
36.5 to 37.4 C	93.8	167	97.6	167
37.5 to 38.4 C	4.5	8	1.2	2
38.5 to 39.5 C	1.7	3	1.2	2
	100	178	100	171

This comparison, while speaking for the milder reactions following inoculation of the sensitized vaccine, was not considered conclusive for the reason that the conditions were not exactly the same both years. A greater proportion of the subjects in 1913 were men, and at that time the word was out that the reactions were expected to be milder than the year before. Moreover, the dosage of the sensitized vaccine, according to the method of preparation at that time, amounted to about one-third less than the dosage now employed, that is, it was approximately 500 million to the cubic centimeter.

Last year, therefore, at the suggestion of Professor Gay and Dr. W. A. Sawyer,[4] director of the State Hygienic Laboratory, it was decided to reinvestigate the subject of reaction severity for the two methods under exactly parallel conditions; and also to attempt a measurement of the relative efficiency of the two types of vaccination, as gaged by the cutaneous typhoidin test.

The army vaccine used was a fresh supply from Washington obtained through the courtesy of Capt. Henry J. Nichols of the Letterman General Hospital. It was administered within about six to eight weeks after the date of its manufacture.[5] The sensitized vaccine

4. Since this work was begun an important report has been contributed by Sawyer (Jour. Am. Med. Assn., 1915, **65,** 1413), who collected from physicians in California data concerning 4,967 persons vaccinated with sensitized vaccine and 2,906 who had been given other vaccines of the general type corresponding to the Army and Navy preparation. Contrary to expectations, the average clinical impressions concerning reaction severity showed no decided difference between the two types of preparation.

5. Nichols (Jour. Exper. Med., 1915, **22,** 780) has reported an apparent relation between the age of the vaccine and its toxicity.

was that supplied by the State Hygienic Laboratory. This was also a fresh preparation, the manufacture of which was completed from six to ten weeks before administration. Care was taken to shake the vaccine before administration, and the usual precautions against vaccinating during menstruation or illness were observed. The injections were made subcutaneously about the insertion of the deltoid. The subjects consisted of nineteen nurses, twenty medical students, twenty-seven members of the staff and help in the University Hospital, and

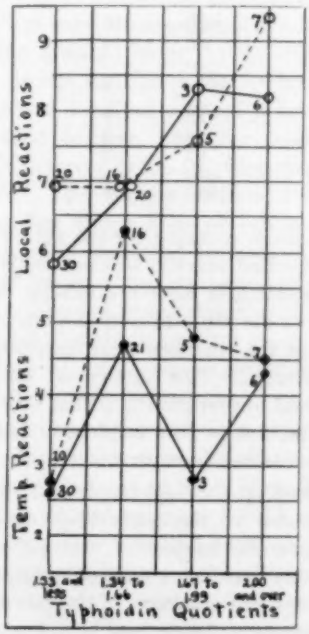

Fig. 1.—The relation between the severity of the local and general reactions following antityphoid inoculation to the previous typhoidin quotients of the subjects. The dots indicate temperature reactions, circles local reactions, solid lines those who received army vaccine, and broken lines those who received sensitized vaccine. At the bottom are indicated the grades of typhoidin quotients; the numbers at the left indicate tenths of a degree centigrade above 37 for the temperature reactions and also grades of local reactions according to the formula in the text. Numbers connected with the dots and circles indicate numbers of individuals on which the corresponding average reactions are based.

twenty dental and pharmaceutical students; fifty-three were men, thirty-two women, eighty-five in all, most of whom were young adults, a few middle aged.

Since there are two chief differences between the two methods

(preparation and dosage of the vaccine, and interval of administration) the subjects were divided into four groups, as follows: Group 1 received army vaccine at two-day intervals; Group 2 the same at ten-day intervals; Group 3 received sensitized vaccine at two-day intervals; and Group 4 the same at ten-day intervals.

The dosage for the army vaccine was always 0.5 c.c. (500 million) for the first dose and 1 c.c. for each of the other two doses; and for the sensitized vaccine 1 c.c. (equivalent to about 750 million) at each of the three doses. These unequal doses of the two vaccines were given because it was desired to compare the methods as they are being used.

Care was taken in forming the groups to have them all as equal as possible both in numbers and in composition, that is, containing approximately the same percentage of males and females, of those who

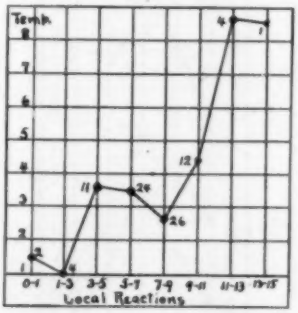

Fig. 2.—The relation between the severity of local reactions and temperature reactions following vaccination. The facts shown may be expressed thus: Among twenty-four subjects whose local reactions following the three inoculations averaged from 5 to 7 the average of highest recorded temperature following the three inoculations was 37.35 C.; among twenty-six subjects, etc.

had previously had typhoid fever or antityphoid vaccination and of those who had not, of nurses, of medical students, of dental and pharmaceutical students and of institutional help. The administration to all four groups was started at the same time, and the subjects were not told which vaccine they were receiving.

Thermometers were supplied and all were required to keep a temperature record, recording the readings as nearly as possible every three hours. Inasmuch as our experience has led us to suspect a considerable amount of suggestion in the reports of symptoms following vaccination, it was decided to use the temperature records alone as a basis for estimating the severity of the general reactions. In thus limiting the analysis it is of course recognized that the temperature is

but one symptom, and that undoubtedly certain subjects are made quite uncomfortable without a corresponding elevation of temperature. It is equally true, however, that the fever group includes the vast majority of those who suffer anything more than slight malaise or body aches, and that practically all those with no symptoms have no rise of temperature. The temperature records were found to agree with the subjects' valuation of their subjective symptoms when the results of the three inoculations were compared in these two ways (Figs. 4 and 5).

Likewise, in recording the severity of local reactions, the usual terms "slight," "moderate," and "severe" were replaced by definite measurements of the size of the local area of redness and of the

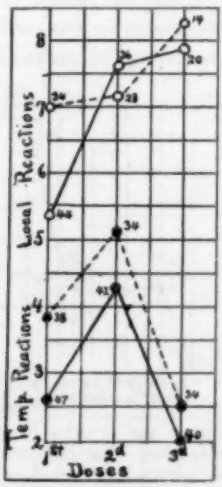

Fig. 3.—The relation of the vaccine used to the severity of reactions. Dots, circles and lines have the same significance as in Figure 1.

increase in circumference of the arm; even though here again it may not always be true that the amount of local discomfort is commensurate with the swelling and redness. At the time of administering the vaccine the circumference of the relaxed and loosely hanging arm was measured at the level of the needle puncture, and the next day this measurement was repeated. With an ordinary reaction the arm increases from 3 to 10 mm. in circumference. In order to obtain a single figure to represent the local reaction, this circumference increase in millimeters was averaged with the diameter of the red area measured in centimeters, according to the following equation:

$$\text{Local reaction} = \tfrac{1}{2}\left(10 \times \text{increase in arm circumference} + \sqrt{\text{longitudinal} \times \text{transverse diameter of red area}}\right)$$

Before receiving the first dose of vaccine, each subject was given a typhoidin skin test, using the dry typhoidin powder according to the technic previously described.[6] Two weeks after beginning the vaccine administration the test was repeated; and again at three weeks, four weeks, five weeks, and from eight to ten months after the first dose of vaccine. The results of these tests were always read after about twenty-four hours and recorded not as merely "positive" or "negative" but as "typhoidin quotients,"[6] that is, the diameter of the typhoidin areola divided by that of the control. The technic was kept as uniform

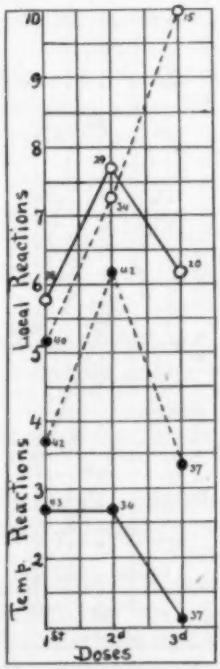

Fig. 4.—The relation of the interval between inoculations to the severity of the reactions. Dots and circles have the same significance as in Figure 1. Solid lines indicate ten-day schedule, broken lines two-day schedule.

as possible throughout the series of tests, and the same stock of typhoidin and control powders was used throughout. The measurements were made with a machinist's gage, and usually without knowing to which group the subject belonged.

1. *Relation Between Typhoidin Tests and Severity of Subsequent Vaccination Reactions.*—For showing this relation the record cards

6. Kilgore: The Archives Int. Med., 1916, **17**, 25.

were arranged in the order of the typhoidin quotients at the beginning of the experiment, and on this basis separated into four classes with typhoidin quotients respectively 1.33 and under, 1.34 to 1.66, 1.67 to 1.99, and 2 and over. In each of these divisions those who received army vaccine were separated from those who received sensitized vaccine, and the average of the local reactions and of the general reactions determined, the reactions following all three doses being first averaged

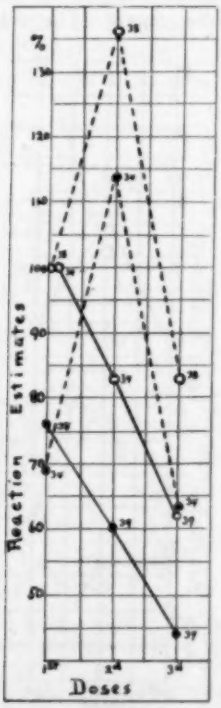

Fig. 5.—Same as Figure 4 except that the subject's estimates of their general and local reactions are used as the basis of comparison instead of temperature and arm measurements; the first reactions were taken by each subject as 100 per cent.

together for each subject. The results are shown in Figure 1, where the dots indicate temperature reactions, circles local reactions, solid lines those who received army vaccine, and broken lines those who received sensitized vaccine. In this figure, as well as those which follow, the numbers opposite the dots and circles indicate the number of persons on which the corresponding averages are based. It will be seen that the smallest local and general reactions occurred in those

with the lowest typhoidin quotients; that is, if the typhoidin quotient is regarded as a quantitative index of immunity against typhoid fever, the least discomfort from antityphoid vaccination was experienced by those most in need of protection. The severest local reactions occurred usually in those with highest typhoidin quotients. It will be noted, however, that the average of highest temperatures occurred in subjects with typhoidin quotients of midvalues, that is, from 1.34 to 1.66, and that no marked difference in this relation appears between the experience of those who took army vaccine and those who were given sensitized vaccine. Possibly in a larger series the highest average temperatures would be found associated with the largest preliminary typhoidin quotients.[7]

2. Relation Between the Severity of the Local and Temperature Reactions Following Vaccination.—On the other hand, we have no assurance that the local and constitutional reactions following vaccina-

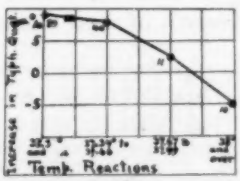

Fig. 6.—The relation between the severity of general reactions and the increase in typhoidin quotients during the next five weeks. Numbers at the left represent percentage gain in typhoidin quotients over the quotient obtained in the previous test; those at the bottom indicate the averages of the highest temperatures recorded after each of the three inoculations in each subject.

tion are due to the same allergic mechanism. The divergence of the curves representing general and local reactions in Figure 1 suggests a possible tendency for the severer local reactions to be more often associated with medium temperature. In order to test this association directly the subjects were divided into eight groups according to the average local reaction in each case following the vaccinations. As before, in each group the average temperature reaction was determined by averaging the highest temperatures recorded for each subject following each of the three doses of vaccine, and then taking the mean of all these averages. It will be seen from Figure 2 that the apparent

7. The general average of temperature reactions in the twenty-one subjects with preliminary typhoidin quotients of 1.67 or over is 0.42 C. According to the formula $E = \pm 0.6745 \frac{\sigma}{\sqrt{n}}$ (Davenport: Statistical Methods with Special Reference to Biological Variation, John Wiley & Sons, New York, 1914) the probable error of this average is ± 0.09 C. It is obviously impossible, therefore, to form any definite conclusions from the downward tendency toward the end of these curves.

tendency is for the highest temperatures to be associated with the severest local reactions and vice versa.[8] The apparent conflict between the facts represented by Figures 1 and 2 may easily be due to the paucity of observations.

3. *The Influence of Typhoid Fever or Vaccination on the Severity of Reactions Following Subsequent Antityphoid Vaccination.*—Not infrequently, on second vaccination, after an interval of one or two years the reaction is considerably more severe than at first; and the general impression has been that second vaccinations are likely to be much more disagreeable. Twenty-three subjects responded to a request to express roughly in figures the relative severity of their symptoms at this time and at the time of a previous vaccination. In nineteen out of this twenty-three the vaccination previously received was sensitized, and in only nine of them was the present administration of the same type. Some of these subjects had received their first vaccination when the method of preparing the sensitized vaccine made the dosage smaller than that now used. Analysis of these replies shows that if the pre-

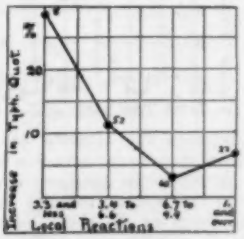

Fig. 7.—The relation between the severity of the local vaccination reactions and the gain in typhoidin quotient during the next five weeks. Same as Figure 5 except that the bottom numbers indicate grades of local reactions.

8. Since this compilation was made another series of sixty-three persons have been vaccinated. They belonged to the same class of subjects; forty-eight were male and fifteen female, and all were inoculated in the course of one week. In the order in which they appeared for the first dose, every other one was given sensitized vaccine (No. 805, manufacture completed four months previously) and every other one army vaccine (mostly No. 171, manufacture of which was completed from four to five weeks previously, a few of the second and third doses being from ampules several months old). The subjects were not told which vaccine they were being given, and the records of temperatures and local reactions were kept and analyzed as before. Since it was felt that the effect of the inoculation interval was fairly well established (see fifth section of this paper), and it was necessary to finish the work shortly, all were vaccinated according to the rapid schedule, every other day, except in thirteen persons, for whom it was more convenient to take the last dose after an interval of four days, that is, one week after the first dose. The figures from this second series substantiate Figure 2, since the average of highest temperatures of those with local reactions below 10 is 37.34 C.; of those with local reactions of 10 or over, 37.55 C.

vious experience is counted as 100 per cent., the general reactions at the present time averaged 197 per cent. and the local reactions 433 per cent. These figures express the general impression noted above, but they are necessarily very rough estimates, and it is conjectural how much the comparisons have been warped by the soothing influence of time and the freshness of the recent sting.

Also, from the relation described above of the reaction severity to the preceding typhoidin test, it would be expected that the less severe reactions would occur in those with negative history, especially since it has been shown[8] that the typhoidin test does bear a certain relation to the previous history of typhoid fever or vaccination. In the present experiments, however, the comparison of the average reactions of forty-eight subjects with negative history and of thirty-seven who had received antityphoid vaccination within the previous three years, or who had had typhoid fever, is as follows:

	Mean of Highest Temperatures, C.	Mean of Local Reaction
Negative history	37.33	7.3
History of typhoid or vaccination	37.36	6.5

The differences between these averages are too small for argument either way;[9] and while the series is not large enough to warrant final conclusions, it gives ground for strong suspicion that, other factors excluded, the supposedly greater average severity of symptoms following second vaccination is overrated, if it exists at all. After an interval of a year or two a number of subjects find a second immunization definitely less annoying.

4. *The Relation of the Vaccine Used to the Severity of Reactions.*—For this comparison the first two groups, which received army vaccine, were separated from the second two, which were given sensitized vaccine. Figure 3 (in which the symbols have the same meaning as in Figure 1) shows the relation of the local and general reactions following each of the three doses. Here again the results were contrary to our expectations, for in every instance except the local reactions following the second dose the higher averages for both local and temperature reactions occurred in the group which received sensitized vaccine. The differences, to be sure, are not very great, and in a larger

9. In the second series (Footnote 8) were forty-six with negative history and seventeen who had had typhoid fever or antityphoid vaccination within three years. The reaction differences between these two groups are as follows:

	Mean of Highest Temperatures, C.	Mean of Local Reaction
Negative history group	37.44	7.4
History of typhoid or vaccination	37.53	8.7

These differences, though slightly larger than in the first series and though they correspond with the prevailing notion of greater severity of second immunizations, are not large enough to modify essentially the opinions expressed above.

series it is possible that the relation would be reversed.[10] Obviously, differences in the strains from which the vaccines are derived may also affect the toxicity. But after this comparison involving eighty-five cases about equally divided (forty-seven receiving army vaccine, thirty-eight sensitized vaccine) it is not to be presumed that a larger series inoculated with the vaccines here used would show the decided difference we had expected to find in favor of the sensitized vaccine. The higher dosage of the army vaccine has also to be taken into account. With fresh preparations, therefore, the uncomfortable effects of the two vaccines are probably about equal.

10. In the second series (Footnote 8) the relation is reversed, thus:

	First Dose		Second Dose		Third Dose	
	Army V.	Sens. V.	Army V.	Sens. V.	Army V.	Sens. V.
Mean of highest temperatures....	37.33	37.32	37.86	37.52	37.39	37.38
Mean of local reactions.....	8.8	7.3	7.1	7	9.6	6.7

The differences, it will be seen, are small, and do not warrant change in the deductions stated after the first series. If the two series are combined the results are as follows:

	First Dose		Second Dose		Third Dose	
	Army V.	Sens. V.	Army V.	Sens. V.	Army V.	Sens. V.
Mean of highest temperatures....	37.45	37.51	37.81	37.61	37.56	37.53
Mean of local reactions.....	5	5.5	5.4	5.9	4.5	3.8

As a measure of the variability of the material and hence of the reliability or "precision" of the results given by the averages exhibited in Figure 3, the probable errors and "standard deviations" were worked out for the temperature averages following the first inoculation, using the formulae E of $M = \pm 0.6745 \frac{\sigma}{\sqrt{n}}$; and σ of $M = \sqrt{\frac{S}{\sqrt{n^3}}}$ (Davenport: Footnote 7). The probable error of the average of highest temperatures following first inoculations of sensitized vaccine was found to be $\pm 0.038 + C.$, that is, the average of 37.39 C. for these thirty-eight subjects has about equal chances of being nearer or farther than 0.038 C. from the truth, as it would have been established by many thousands of observations. The corresponding probable error for the group of forty-seven who received army vaccine is 0.027 C. According to the formula $A_1 - A_2 = \sqrt{E_1^2 + E_2^2}$ (Davenport: Footnote 7), the probable difference between the two averages is 0.047 C. It will be seen that these probable errors are not large in comparison with the separation of the two averages, a fact which creates a strong suspicion that the sensitized vaccine used at this time was really more pyrogenic than the army vaccine. A definite conclusion to this effect should not be made, however, without a consideration of the possible error. It is known that in frequency distributions of the symmetrical or moderately symmetrical type, such as these temperature averages might be expected to form if the work here reported were repeated many times on fresh material of the same kind, a range of six times the standard deviation constitutes the practical limits of variation, that is, it includes about 99 per cent. of all values of the variable (Yule, G.: Introduction to the Theory of Statistics, Charles Griffin & Co., London). The standard deviations of these averages are respectively 0.025 and 0.018 C. Six times the larger of these (0.025) is 0.15 C., which is a little more than the difference between the two averages. So that there is a possibility (though rather remote) that these two averages could have been derived from similar material; that is, that the showing of severer general reactions following the sensitized vaccine represents a simple "fluctuation of sampling" and not a real difference in the effects of the two vaccines.

5. *The Relation of the Interval Between Inoculations to the Severity of the Reactions.*—For showing this relation, Groups 1 and 3 (forty-two subjects), in which vaccine was administered every other day, are compared with Groups 2 and 4 (forty-three subjects), in which the dosage interval was ten days. The comparison is shown in Figure 4, where the dots indicate temperature reactions, the circles local reactions, solid lines the ten-day schedule, and broken lines the two-day schedule. It will be seen that the general reaction following the first dose was a little more severe in the two-day group than in the ten-day group, a difference not to be accounted for by the difference in dosage interval which followed. Allowance for this difference should be made, therefore, in comparing the results of the second and third inoculations in the two groups. After making this allowance, however, a substantial difference remains in favor of the ten-day schedule as the more comfortable.

The local reactions are approximately the same in the two groups for both the first and second inoculations, while following the third inoculation the two-day group, according to the measurements taken, had their severest reactions, and the ten-day group averaged considerably less. The practice was to vaccinate, about the insertion of the deltoid, the first time in the left arm, the second time in the right arm, and the third time in the left arm again. Fresh areas for inoculation were therefore used for the first and second doses, while for the third the first area was reinoculated. Thus in the two-day group the third injection was into an area which had been injected only four days previously; in the other group the interval was twenty days. This fact probably accounts for the difference in the local reactions following the third doses.

It is quite possible, however, that these measurements of the increase in arm circumference and size of the red area (especially the latter) in the arms reinoculated after a four-day interval do not accurately represent the relative discomfort to the subjects. In fact, the average estimate of the subjects themselves was not in agreement with this comparison of second and third local reactions. They were asked to state roughly in figures the relative severity of local and general symptoms following the three inoculations, taking the first as 100 per cent. The results are shown in Figure 5, where the dots, circles and lines have the same significance as in Figure 4. It will be seen that the estimates agree quite closely with the general reactions interpreted in terms of the highest temperatures, the temperature reaction following the second dose being specially high in the two-day group. The second local reaction was most severe according to the average testimony of the two-day group. In the ten-day group the averages for

both local and general reactions were thought to become less severe with each succeeding dose. The averages of the general reactions following the first dose are less than 100 per cent., because in some cases no general symptoms were noted at this time, and the reaction was, therefore, rated 0 per cent. In such cases, if any symptoms followed the second dose it was then called 100 per cent.

6. *The Influence of the Vaccine Used and of the Dosage Interval on the Extent and Rapidity of Immunity Production.*—It was hoped to obtain from the successive cutaneous typhoidin tests following vaccination some indication of which vaccine and which dosage interval produced immunity the more promptly or certainly. For the purposes of this comparison the typhoidin quotients obtained in these tests were expressed as percentage gains or losses, as compared with the preliminary typhoidin quotients. Thus, if the preliminary quotient was 1.5 and one of the later quotients 2, the result was put down as 33 per cent. gain, while if the later quotient was 1.25 there was a loss, which was recorded as —17 per cent. The algebraic sum of these plus and minus percentages was divided by their number to obtain the averages.

The numbers not being large enough (owing to the closing of the school year, many of the later tests were not obtained) to make profitable separate comparisons of the different weekly tests in each group, the results of second, third, fourth, and fifth weeks have all been averaged together and show the following comparisons:

In Group 1 (army vac., 2-day interval) gain in quot. (av. of 40 tests) = 13%
In Group 2 (army vac., 10-day interval) gain in quot. (av. of 40 tests) = 3%
In Group 3 (sens. vac., 2-day interval) gain in quot. (av. of 35 tests) = 5%
In Group 4 (sens. vac., 10-day interval) gain in quot. (av. of 35 tests) = 11%

The average gain for all those who received vaccine every other day was 9 per cent., as compared with 7 per cent. for those on the ten-day schedule. The average for all those who received army vaccine was 8 per cent., and exactly the same for all those who received sensitized vaccine.

From eight to nine months after the vaccinations, as many as possible of these subjects were given another cutaneous typhoidin test, using the same stock of typhoidin and control powders. These typhoidin quotients were similarly compared with the prevaccination quotients, and the averages in each group are as follows:

In Group 1 (army vac., 2-day interval) gain in quot. (av. of 15 indiv.) = 1 %
In Group 2 (army vac., 10-day interval) gain in quot. (av. of 11 indiv.) = 4.5 %
In Group 3 (sens. vac., 2-day interval) gain in quot. (av. of 13 indiv.) = 20 %
In Group 4 (sens. vac., 10-day interval) gain in quot. (av. of 12 indiv.) = 10 %

Again there is no marked difference between the two-day and ten-day groups, but those who received sensitized vaccine now show considerably greater average gain in typhoidin quotients than those who were given army vaccine.

This difference is not referable to differences in composition of the groups, for all contain about the same proportion of individuals who had received their first and only typhoid vaccination eight to ten months previously and those who had also had still earlier immunizations (the latter comprised 50 per cent. of the first two groups and 54 per cent. of the second two groups). Moreover, the greater gain in typhoidin quotients among those who received sensitized vaccine cannot be accounted for by a closer relation in this group between the immunizing vaccine and the typhoidin. The strain of organism used in preparing the typhoidin was the Dorset strain, while the army vaccine is prepared from the Remling strain, and the sensitized vaccine from strains isolated from four cases in California.

The table as it stands, therefore, suggests that sensitized vaccine is considerably more potent than army vaccine in producing well marked typhoidin skin tests eight to ten months after vaccination.

Before a definite conclusion to this effect can be drawn, however, it is necessary to consider the amount of variation in the figures from which these averages are derived and the strength of the probabilities that similar differences would be present if the groups were much larger. The high average gain of 20 per cent. in Group 3 would be reduced to 9 per cent. by the omission of one remarkably high quotient caused by a very wide but faint outer areola about the test spot.[11] The following table shows for each of the average typhoidin quotient gains its probable error and practical limits:[12]

	Mean Gain in Typh. Quot., %	Prob. Error of Mean, %	Practical Limits of Variation of Mean., %
Group 1	1	6	—18 to 36
Group 2	4.5	5	—17 to 25
Group 3	20	9	—20 to 60
Group 4	10	7	—21 to 41
Groups 1 and 2 (army vac.)	2	4	—16 to 20
Groups 3 and 4 (sens. vac.)	15	6	—10 to 40

It will be seen that by this consideration of the probable errors and practical limits, what at first appeared to be a rather striking and definite difference in favor of the sensitized vaccine is shown to be easily within the territory of experimental error. Evidently it would

11. Kilgore: Elsewhere in this number of this journal.
12. That is, a range of six times the standard deviation, Footnote 9.

be a mistake to base conclusions on the differences between these averages unless the differences were much greater or the series much larger or unless there were much more uniformity among the individual typhoidin quotient gains.

It is clear, therefore, that the cutaneous typhoidin test has revealed no superiority connected with the three-day or the ten-day inoculation interval, and in the first month after vaccination no difference between the two types of vaccine used. Eight to ten months later there is a probability (unfortunately quite a weak one) that those who have received sensitized vaccine will show the more marked cutaneous reactions to typhoidin. If the average typhoidin quotient of a group of individuals is assumed to be proportional to their resistance against typhoid fever, as was suggested by the finding of a higher average quotient among immunes than nonimmunes,[6] the observations here recorded may be looked on as favorable to the sensitized vaccine as the more efficient means of producing immunity. It must be emphasized, however, that as yet there is no definite warrant for such an assumption in regard to immunity, even if the higher typhoidin quotient following sensitized vaccine administration were borne out by adequate statistics.

7. The Relation Between the Severity of the Reactions Following Vaccination and the Subsequent Gain in Typhoidin Quotients. — By using the postvaccination typhoidin tests in the manner just described, the cases were separated into four classes according to the severity of the temperature reactions: those whose highest temperatures following the three vaccinations averaged (1) 37.33 C. or less, (2) from 37.34 to 37.66 C., (3) from 37.67 to 37.99 C., and (4) 38 C. or over, and the average increase in typhoidin quotients was calculated for each class. The results are shown in Figure 6, where the numbers at the bottom indicate the four grades of temperature reactions and those at the side the percentage gain in typhoidin quotients during the following five weeks. The results of the typhoidin tests from eight to ten months after vaccination are not shown, since the observations were so few that the averages were markedly discordant.

In Figure 7 the same sort of comparison is shown with the cases divided according to the severity of the local reactions, the numbers at the bottom indicating grades of local reaction obtained according to the formula already given.

Figures 6 and 7 suggest that those who have the highest temperatures and the greatest amount of arm swelling and redness from the vaccination are the ones who show the least increase in their typhoidin quotients. Or, conversely, that if it is true that the typhoidin test

applied to groups gives a quantitative index of typhoid immunity, those who suffer least discomfort from the vaccination derive the greatest benefit from it. This of course is the result to be anticipated from observations already made. For the group which has the best chances of showing the greatest average gain in typhoidin quotient is obviously the group with the low preliminary quotients; and these are also (Fig. 1) the ones with the lesser reactions following vaccination.

The numbers are not large enough to make profitable a separate comparison for the different vaccines or methods of administration.

CONCLUSIONS

Final conclusions are not warranted from the number of observations in this series, especially since in some particulars they would be at variance not only with what seemed to be my own experience, but also with that of Gay, Force, and others. Since, however, some changes have been made in the dosage and preparation of the sensitized vaccine since our former impressions were received, and since more than the usual precautions were taken at this time to eliminate the personal equation in the results, the following findings may be put forth with the understanding that they are to be given weight only in accordance with the number of observations on which they are based:

1. The higher the typhoidin quotient in a given person, the greater his chances of a severe reaction to antityphoid inoculation.

2. The severer local reactions to vaccine tend to occur in those subjects with the higher temperature reactions.

3. The supposedly more severe average reaction to antityphoid inoculation of subjects who have previously had the treatment is probably overrated.

4. The use of army vaccine or sensitized vaccine sediment if the preparations are fresh makes little if any difference in the average local and temperature reactions.

5. When either type of vaccine is administered every other day the temperature reactions following the second and third doses are likely to be more severe than when the injections are ten days apart. A difference in the local reactions is not so clear cut. The average impression of the subjects vaccinated every other day is that the second injection gave the greatest local and general discomfort and the third least. The average member of the ten-day group feels that both general and local reactions were less with each succeeding dose.

6. The typhoidin test failed to show any noteworthy differences in effectiveness between the two-day or ten-day schedules, and, in the

first few weeks, between the two vaccines used. Later the typhoidin quotients were higher in those who had received sensitized vaccine, but the differences are not decided enough to support definite conclusions that this is the rule.

7. According to the typhoidin test it is suggested that the ones who react least to vaccination tend to profit most by its administration.

THE AGGLUTININS AND COMPLEMENT-FIXING ANTIBODIES IN THE SERUM OF PERSONS VACCINATED AGAINST TYPHOID FEVER*

K. F. MEYER AND EUGENE S. KILGORE
SAN FRANCISCO

During the last few years numerous reports have appeared on the value of the Widal reaction in vaccinated persons. Most of these studies suffer from lack of uniformity of technic or from faulty conclusions derived from a study of selected cases only. In the European armies the extensive use of typhoid vaccines of varying antigenic value and different modes of preparation has especially called forth numerous publications on the value of serologic tests as a means of ascertaining the grade of immunity present. Unfortunately, the results are not comparable on account of the diversity of the preparations and of the methods used in the different countries. Most of the writers consider only the agglutination test (their results will be discussed in connection with ours). Felke[1] and also Hage and Korff-Petersen,[2] however, report as well on the value of the complement fixation test; thus Felke claims to be able to distinguish patients who had had typhoid fever from those who had been vaccinated, by the absence of complement fixing antibodies in the serum of the latter. Nine months after the last vaccination, however, Hage and Korff-Petersen found in a few of the persons decided fixation of the complement.

Wollstein[3] and Howell,[4] in this country, studied carefully the various immune bodies and in four patients and two patients, respectively, vaccinated with Russell's preparation, according to the United States Army method. Wade and McDaniel,[5] Moon,[6] Hamilton,[7] Rüdiger

* Submitted for publication Aug. 9, 1916.

* From the George Williams Hooper Foundation for Medical Research, and the Department of Medicine, University of California Medical School, San Francisco.

1. Felke: Die Komplementablenkung als Reaktion zur Unterscheidung zwischen den Seren Typhuskranker und gegen Typhusgeimpfter, München. med. Wchnschr., 1915, **62,** 578.

2. Hage and Korff-Petersen: Typhusschutzimpfung und Typhusdiagnose, Deutsch. med. Wchnschr., 1915, **45,** 1328.

3. Wollstein, M.: The Duration of the Immune Bodies in the Blood after Antityphoid Inoculation, Jour. Exper. Med., 1916, **16,** 315.

4. Howell, Katherine: Observations on the Production of Antibodies after Antityphoid Inoculation, Jour. Infect. Dis., 1916, **19,** 63.

5. Wade, E. M., and McDaniel, O.: Observations on the Widal Reaction Following the Administration of Typhoid Vaccine, Am. Jour. Pub. Health, 1915, **5,** 136.

6. Moon, V. H.: Experimental Immunity in Relation to the Agglutination Reaction in Typhoid, Jour. Am. Med. Assn., 1913, **60,** 1764.

7. Hamilton, C. D.: The Effect of Typhoid Vaccination on the Widal Reaction, Jour. Am. Med. Assn., 1915, **65,** 1873.

and Hulbert,[8] and others tested the Widal reaction in those vaccinated with preparations of their own make. In these instances the microscopic agglutination test was employed and no definite quantitative determinations were attempted.

Thus far no data are available concerning the serum reactions in human beings vaccinated with the sensitized, detoxicated vaccine sediment of Gay and Claypole.[9] From experimental work done on rabbits by Nègre[10] and Löwy[11] with living sensitized bacilli, and by Gay and his co-workers with the killed sensitized typhoid bacilli, it has become known that animals so vaccinated develop agglutinins only in moderate concentrations as compared with those in which the untreated typhoid antigen is used. On the other hand, according to Nègre and Löwy, the serums of animals immunized with sensitized vaccines contain the complement-fixing antibodies and the bactericidal substances in larger, or at least in the same, amounts as compared with those treated with nonsensitized vaccines.

The growing importance of typhoid immunization, the continued uncertainty in regard to the best type of vaccine, optimum interval between doses, and the interval after which revaccination becomes advisable, as well as the desire of physicians and laity for a practical test of typhoid immunity, make important any work which may throw light on this subject. In view, therefore, of the unsettled state of the literature concerning typhoid serologic changes, it was considered important, in connection with a new series of cutaneous typhoidin tests (reported by one of us elsewhere in this number of this journal) to investigate in the same subjects at the same time the phenomena of agglutination and complement fixation.

The subjects consisted of ninety-eight students, nurses and others connected with the University of California Departments of Medicine, Dentistry and Pharmacology; most of them were young adults and all in apparently good health. Seventeen had had typhoid fever from three and one-half to twenty-five years ago (in most cases not proved by biologic methods); twenty-six had received army vaccine[12] from

8. Rüdiger, G. F., and Hulbert, Robert: Is Blood as Reliable as Fresh Serum in Making the Widal Test? Am. Jour. Pub. Health, 1914, **4**, 113.

9. Gay, Frederick P., and Claypole, Edith J.: An Experimental Study of Methods of Prophylactic Immunization Against Typhoid Fever. Studies in Typhoid Immunization, V, THE ARCHIVES INT. MED., 1914, **14**, 671.

10. Nègre, L.: Rècherches comparatives sur la disparation des reactions humorales des lapins immunisés avec des bacilles typhique vivantes sensibilesés, tués par la chaleur et tués par l'éther, Compt. rend. Soc. de biol., 1913, **75**, 412; ibid., **74**, 1177.

11. Löwy, O.: Immunkörperbildung verschiedenartiger Typhusimpfstoffe, Deutsch. med. Wchnschr., 1915, **45**, 1277.

12. The army vaccine was obtained through the courtesy of Capt. Henry J. Nichols of the U. S. Army Medical Corps. The details relative to these vaccinations are given by one of us elsewhere in this number of this journal.

three to eight months previously, and thirty-seven had been given sensitized vaccine[13] within the same time. The term "vaccination" as here used implies in all cases the full three inoculations. In the use of both types of vaccines about one-half the persons had been inoculated at intervals of three days and the others at ten-day intervals. These dosage intervals are not specified in the tables herewith, for, as Cahn-Bronner[14] has recently shown, irregularity of vaccination has no influence on the formation of antibodies.

AGGLUTINATION TESTS

Method.—The use of a uniform, standardized antigen for comparative tests is of the greatest importance. Dreyer and Walker[15] and co-workers have clearly pointed out the fallacies of the old microscopic method and the unreliability of the agar suspensions, and for years it has been our practice to use broth cultures in tests with organisms of the paratyphoid group.[16] Liebig's broth cultures of the typhoid bacillus were treated either with phenol (0.5 per cent.) or with formaldehyd solution (0.1 per cent.) and carefully standardized with rabbit immune serums. Liebig's broth, obtained from one and the same lot of preparations and having a reaction of 0.85 per cent. (p_H 7.2) was used. All the strains of *Bacillus typhosus* had been previously subcultivated in Liebig's broth daily for two weeks. The typhoid strains employed included the army strain (Rawlings), and four others (M., L., B., and Sch.), which were known to be present in the sensitized vaccine sediment. Separate series for each strain were set up and the average agglutination titer was calculated from the five agglutination reactions of each serum. This average is given in the tabulated results.

Fresh and perfectly clear serum from proper dilutions in amounts varying from 0.1 to 0.01 c.c. was introduced with capillary pipets into narrow, suspended tubes, and to each 1 c.c. of the standardized antigen was added. After carefully shaking, the tubes were incubated for two hours at 37 C., and the results noted. Final readings, however, were made only after an interval of twelve hours. In the tables is recorded only complete agglutination in twelve hours with a perfectly clear, supernatant fluid.

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13. The regular product supplied during the last three years by the California State Hygienic Laboratory.

14. Cahn-Bronner, C. E.: Typhus Schutzimpfung und Typhusdiagnose bei Geimpften, Med. Klin., 1915, **11,** 964.

15. Dreyer, Georges: Widal's Reaction with Sterilized Cultures, Jour. Path. and Bacteriol., 1909, **13,** 332. Walker, E. W. Ainley: A Note on Widal's Reaction with Standardized Agglutinable Cultures, Lancet, London, 1916, **1,** 17.

16. Meyer, K. F., and Boerner, F.: Studies on the Etiology of Epizootic Abortion in Mares, Jour. Med. Research, 1913, **29,** 325.

Table 1 contains a summary of the results obtained in ninety-two cases, which are divided into five large groups, according to their histories. The first group consists of twenty-three persons who had been vaccinated with army vaccine from three to eight months previously. Of these, twelve had then been vaccinated for the first time, while eleven had also had a previous course of immunization with either sensitized or army vaccine.

TABLE 1.—PERCENTAGE OF AGGLUTINATION REACTIONS

Group	Vaccine Preparation	Time Interval	Dilutions of Serum						No. Cases
			1:40	1:60	1:80	1:100	1:200	1:400	
1	Army vaccine, first time...	8 mo.	100	80	60	50	50	10	10
	Army vaccine, first time...	3 mo.	100	100	100	50	50	.....	2
	Army vaccine, repeated inoculations	8 mo.	90.9	55.5	36.3	27.2	9	9	11
2	Gay-Claypole sensitized vaccine sediment, first time	7 to 10 mo.	57.1	21.4	14.2	14.2	.....	.....	14
	Gay-Claypole sensitized vaccine sediment, first time	2 mo.	33.3	.....	.....	.....	.....	.....	3
	Army vaccine, repeated inoculations	8 mo.	70.5	29.4	23.5	5.8	.....	.....	17
	Army vaccine, repeated inoculations	6 mo.	100	.....	.....	.....	.....	.....	1
		2 mo.	100	100	100	.....	.....	.....	1
3	Negative history.....	.....	82.9	11.7	11.7	.....	.....	.....	16
4	Typhoid fever.....	3½ to 25 yr.	60	30	20	.....	.....	.....	10
5	Typhoid fever and vaccinated with army vaccine	6 to 8 mo.	60	40	20	20	20	.....	5
	Typhoid fever and vaccinated with Gay-Claypole sensitized vaccine sediment	6 to 8 mo.	50	50	50	50	.....	.....	2

In the columns under the various serum dilutions are recorded the percentage of cases giving complete agglutination. It will be seen that this group, as a whole, shows a well-marked persistence of agglutinins, regarded either from the standpoint of agglutination in high dilutions or high percentage of individuals having a moderate amount of agglutinins. The slightly greater percentage of high dilution agglutinations among those who had had but one course of immunization depends on too few observations to merit an attempt to interpret it.

The second group consists of thirty-six persons who had been

vaccinated with Gay-Claypole[9] sensitized vaccine sediment from two to ten months previous to the test. For thirteen of them this vaccination was the first and only typhoid immunization; the other nineteen had been immunized one or more times before with sensitized or army vaccine.

This entire group shows a very low agglutination titer. Thus, only 14.2 per cent. agglutinate *B. typhosus* in a dilution of 1 to 100. Over 40 per cent. failed to agglutinate in a dilution of 1 to 40 and, from the records not tabulated, over 23 per cent. of the serums failed to agglutinate the typhoid bacillus even in a dilution of 1 to 20. In this respect the group shows analogies to Group 3, in which neither the history of typhoid fever nor previous typhoid inoculation was obtainable. Some irregular cases may show agglutination in higher dilutions; but, as will presently be shown, the same may also happen in the "negative history" group.

The third group comprises sixteen persons who gave no history of antityphoid vaccination or typhoid fever. With our standardized typhoid antigen the serum of such an individual will rarely agglutinate in a dilution higher than 1 to 40; and this statement conforms well with the average of thousands of tests reported in the literature.[17] It is well known that the agglutinability of the strains employed for such tests will influence the results. Our strains, no doubt, were easily agglutinated. The average of nearly 50 per cent. of the serums gave an agglutination in a dilution of less than 1 to 40 and about 10 per cent. failed to agglutinate the typhoid bacillus. One case, with a negative history, gave an agglutination of 1 to 80 and a marked complement fixation, together with a very high typhoidin quotient (2.29). In view of the undoubtedly large number of undiscovered cases of typhoid fever,[18] it is not improbable that if the facts were known, this case would be classed in Group 4 with the typhoid recoveries.

The fourth group includes ten subjects who gave a definite history of having had typhoid fever from three and one-half to twenty-five years before. The serums of this group behaved, in many respects, like those of Group 3. Thus, the percentage of agglutination is low, only about 40 per cent. of the serums giving negative reactions, or agglutinating in dilutions below 1 to 40. In only two cases was a positive result noted in a dilution of 1 to 80; both of these subjects had typhoid fever from ten to twelve years previously. In some persons therefore, the agglutination titer apparently persists for a long period

17. Fornet, W.: Immunität bei Typhus, Kolle-Wassermann Handbuch d. pathogenen Mikroorganismen, Ed. 2, G. Fischer, Jena, 1914, **3**, 845.

18. Sawyer, Wilbur A.: Ninety-Three Persons Infected by a Typhoid Carrier at a Public Dinner, Jour. Am. Med. Assn., 1914, **63**, 1537.

after an attack of typhoid fever. Donges[19] and others made the same observation, but failed to find that this condition is influenced by another intercurrent disease. But according to the experimental studies of von Wassermann and Sommerfield[20] it is not unlikely that an increase in the agglutinins may occur during the development of an intercurrent infection. No such cause was present, however, in our two cases.

In the fifth group are five persons who had had typhoid fever and who subsequently also had been vaccinated with sensitized vaccine sediment or army vaccine. Some of these had received as many as three courses of inoculations, the last vaccination in all cases being from six to eight months before our tests. From these few observations there is after a few months little apparent tendency of the vaccination to modify the low agglutinin concentration of the typhoid recoveries.

From experimental work on man (Moon[21]) and animals (Cole[22] and others) we may infer that in subjects who have had typhoid fever or antityphoid vaccination a subsequent injection of typhoid vaccine calls forth immune bodies rapidly and in considerable amounts; but that these immune bodies are also quick to disappear. Evidently, in all but one case their subsidence had taken place during the six or eight months between the last vaccination and our tests.

In the chart are shown graphically our most striking serologic findings, that is, the differences between Groups 1 and 2, those who had had army vaccine and those who had received sensitized vaccine. From the results after from three to eight months, it will be seen that the army vaccine appears to have considerably greater influence than sensitized vaccine in promoting the persistence of agglutinins in high concentration. This great potency of the army type of vaccine in stimulating the development of agglutinins has been previously shown by Russell[23] and by Wollstein.[3]

Dissimilarity in technic and in the preparation and dosage of the various vaccines forbid a strict comparison of our results with those of the British and German writers. The army vaccine, however, being a preparation of typhoid bacilli killed by heat, is similar in composition

19. Donges: Ueber die agglutinatorische Kraft des Serums nach überstandener Typhusinfection, Centralbl. f. Bakteriol., 1914, **75,** 174.

20. V. Wassermann and Sommerfeld: Experimentelle Untersuchung über Typhus Schutzimpfung, Med. Klin., 1915, **11,** 1307.

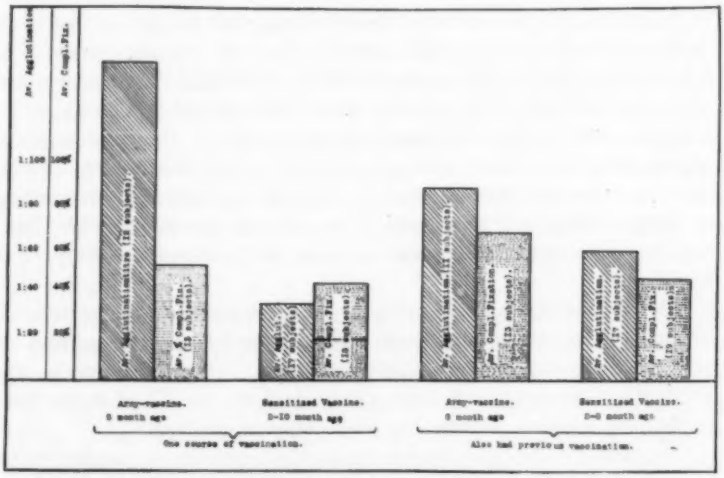
21. Moon, V. H.: Observations on Antibody Formation in Typhoid, Jour. Infect. Dis., 1914, **14,** 56.

22. Cole, R. I.: Experimenteller Beitrag zur Typhusimmunität, Ztschr. f. Hyg. u. Infectionskrankh., 1914, **46,** 371.

23. Russell, F. F.: Antityphoid Vaccination. The Immediate Results of the Administration of 3,600 Doses, Bull. Johns Hopkins Hosp., 1910, **21,** 83.

and antigenic effect to the Wright or Pfeiffer-Kolle vaccine; so that many of the reports concerning agglutinins in vaccinated soldiers may be used for comparison.

In general, our figures, for those who had received army vaccine, are lower than those of the English writers and higher than those of German writers. Stieve,[24] for instance, states that the maximum agglutination which he obtained with serums from soldiers eight to twenty-one days after the last inoculation with Russell's vaccine was 1 to 600. However, we have observations on hand which show that the titer of 1 to 4,000 or 1 to 6,000, obtained with broth cultures treated with formaldehyd, six days after the second inoculation are not at all exceptional.[4]



Graphic showing of agglutination and complement fixation averages with army vaccine and sensitized vaccine.

Dreyer and Inman[25] emphasize the persistence of agglutinins in the blood of vaccinated soldiers and state that they exist for a longer period in the blood than is usually thought to be the case. In persons inoculated with two or more doses of vaccine a higher agglutination titer was noted than in those who received only one dose. Dakeyne[26] came to the same conclusions: he states that a gradual diminution in

24. Stieve, H.: Beobachtungen bei der Typhusschutzimpfung mit dem Russell'schen Impfstoff, München. med. Wchnschr., 1915, **62**, 237.

25. Dreyer, G., and Inman, A. C.: Persistence of Antibodies in the Blood of Inoculated Persons as Estimated by Agglutination Tests, Lancet, London, 1915, **2**, 225.

26. Dakeyne, D. I.: Observations on Some of the Agglutination Reactions of the Blood of Soldiers Inoculated Against Typhoid Fever, Lancet, London, 1915, **2**, 540.

the agglutination reaction results at the end of the eighth month. Dyer[27] found that five months after vaccination fifteen persons out of twenty-eight gave an agglutination in a dilution of 1 to 80, five in 1 to 60, and one in 1 to 320; and not in one instance was an agglutination less than 1 to 40 obtained. Cahn-Bronner[14] made the observation that in a large number of tests with Ficker's typhus diagnostikum, over 50 per cent. of German soldiers still gave an agglutination in a dilution of 1 to 50 after 240 days, and that over 38.5 per cent. reacted in a dilution of 1 to 100, and 23 per cent. in 1 to 200. Klose,[28] Klemperer. Oettinger and Rosenthal,[29] Weichhardt,[30] Ziersch,[31] Dünner,[32] Reiss,[33] and Hage and Korff-Petersen[2] noted the persistence of immune substances in soldiers vaccinated with different preparations.

Wade and McDaniel[5] state, however, that the Widal reaction is of short duration following the administration of typhoid vaccine. In only 16.3 per cent. of the cases was it still present after six months, and after one year only 11.7 per cent. gave a microscopic agglutination in a dilution of 1 to 50. Hamilton,[7] using an equally unreliable antigen, reports that all the vaccinated persons gave an agglutination in 1 to 50 up to the twenty-fourth month following the last injection. According to Bloch and Creuzé,[34] one half of the subjects vaccinated with Chantemesse preparation still gave one year later an agglutination of 1 to 100.

Our results, indicating as they do the large effect on the persistence of agglutinins which may come from variations in the method of preparing the vaccine, constitute an instructive commentary on the conflicting literature, and strongly suggest the need for better controlled experiments in attacking this complex problem.

In view of the considerable amount of variation in agglutination

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27. Dyer, A. W.: The Agglutination Reaction after Antityphoid Inoculation, Indian Jour. Med. Research, 1913-1914, **1,** 728.

28. Klose: Die Gruber-Widal'sche Reaktion bei typhusschutzgeimpften Franzosen und ihre Bewertung für die Diagnosestellung, Arch. f. Hyg., 1915, **74,** 193.

29. Klemperer, F., Oettinger, W., and Rosenthal, F.: Zur Diagnostik und Therapie des Typhus im Felde, Therap. d. Gegenw., 1915, **17,** 162.

30. Weichhardt, W.: Ueber Typhusimmunisierung, München. med. Wchnschr., 1915, **62,** 431.

31. Ziersch, P.: Beobachtungen bei Typhusschutzgeimpften, München. med. Wchnschr., 1915, **62,** 1312.

32. Dünner, L.: Die Bedeutung der Widal'schen Reaktion bei Typhusgeimpften Soldaten, Berl. klin. Wchnschr., 1915, **52,** 59, 683.

33. Reiss: Der Wert der Agglutinations Probe bei Typhusgeimpften, München. med. Wchnschr., 1915, **62,** 1277.

34. Bloch, M., and Creuzé, Pierre: Reactions humorales consecutives a l'emploi du vaccin antityphoide de Chantemesse, Compt. rend Soc. de biol., 1912, **73,** 566.

titer among individuals of the same group and the limited number of observations, it is not possible from our results to make any statement in regard to the rate with which agglutinins disappear from the circulation of vaccinated persons. Klemperer, Oettinger, and Rosenthal[29] report irregularity in the rate of agglutinin subsidence in contrast to the regular, gradual decrease which is noted in cholera vaccination. Cahn-Bronner reported that in different cases the titer declined slowly or rapidly after the eighty-fifth day following the last injection, but that the change was always regular. For example, according to numerous observations, if a case showed a high agglutination four months after the initial vaccination, the decrease in the following months would be slow. On the other hand, in a case with a very low titer, the change to a negative agglutination within the same time interval would be more precipitous. This may be the explanation of the low values obtained in some of our cases of Groups 1 and 2.

Mention should here be made of the possible relationship between the intensity of the reaction following the administration of the vaccine and the subsequent agglutination titer. The early conception of Hetsch and Kutscher[35] that the agglutination titer is influenced by the clinical reaction has again been supported by Dakeyne. On the contrary, Cahn-Bronner, Klose and others fail to find any such relationship.

In our series one subject, on account of the severity of the reaction, was inoculated with only two doses of army vaccine, and her agglutination titer was still 1 to 400 eight months after the last injection. Three other cases, however, with similarly severe reactions, showed a low titer. From these observations it is apparent that to what extent vaccination reactions influence the degree of antibody production cannot be stated with any certainty from the data at hand.

Finally, in the light of the irregular persistence of the agglutinins in the serum of vaccinated persons, the Widal test in its usual clinical form has lost its diagnostic value in these cases. When, however, repeated quantitative determinations are made with the serum of the suspected typhoid patients, a change in the fluctuations of the titer may be of diagnostic significance, as has been shown by Dreyer and his pupils[36] in a large number of cases.

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35. Gaffky, Kolle, Hetsch, and Kutscher: Ueber Typhusschutzimpfungen, Klin. Jahrbücher, 1905, **14,** 124.

36. Davison, Wilburt C.: The Diagnosis of Enteric Fever (Typhoid and Paratyphoid A and B) by Agglutination Tests, Jour. Am. Med. Assn., 1916, **46,** 1297. Klieneberger: Agglutinationstiter bei Infektionskrankheiten, ims besondere Typhus und Paratyphus, Deutsch. med. Wchnschr., 1914, **40,** 1511.

COMPLEMENT FIXATION TESTS

Our method was a modification of the ordinary Wassermann technic, the system being based on the use of a total fluid bulk of 2.5 c.c. of a 1 per cent. blood cell suspension. Because of the reliability of the technic a few details in connection with it may deserve mention.

Lemco[37] broth cultures about eighteen to twenty hours old were used as antigen. Younger cultures are frequently not sufficiently antigenic, and older ones are very anticomplementary. The advantage of these broth cultures over suspensions of extracts has been demonstrated repeatedly by Bordet, Massol and Grysez[38] and others.

The broth cultures were heated for one-half hour at 80 C., and preserved with 1 per cent. glycerin and 0.5 per cent. phenol (carbolic acid). Kept cool and protected from the light, they remained unchanged for the entire month during which they were employed for these tests. Four antigens were used: (1) broth culture of the army strain (Rawlings); (2) broth culture of thirty different strains of *B. typhosus*;[39] (3) broth culture of a strain of *B. coli* isolated from a case of cystitis; and (4) a polyvalent aqueous extract of thirty strains of *B. typhosus* prepared according to Dean.[40] This antigen was used only in some control tests.

The dose of the antigen chosen was four times the antigenic unit as determined by preliminary titrations of the antigen with a standard amount of rabbit immune serum, either 0.1 c.c. or 0.2 c.c. This dose was at least from one fourth to one fifth of the anticomplementary unit, as determined in the preliminary test. The range of the specific antigenic properties of each antigen was further controlled by numerous tests with serums of known antibody content.

The serum was separated from the blood clot by centrifugalization and kept in small vials at refrigerator temperature. Shortly before use they were inactivated at 56 C. for one-half hour. A standard amount of 0.1 c.c. was titrated against decreasing amounts of the antigens, the largest amount being four times the antigenic unit. Furthermore, in about 50 per cent. of the tests decreasing amounts of serum were titrated against a standard amount of antigen. Ordinarily, three such titrations were carried out in the above-mentioned broth cultures.

The antisheep hemolytic serum was used. Complement was fur-

37. Lemco, Method of preparation in, Eyre, T. W. H.: The Elements of Bacteriological Technique, Ed. 2, 1913, 163.

38. Massol, L., and Grysez, V.: Antigènes et anticorps typhiques. Reaction d'inhibition, Compt. rend. Soc. de biol., 1913, **75,** 220.

39. The senior author is indebted to Dr. F. P. Gay for some of the strains of B. typhosus used in this antigen.

40. Dean, H. R.: Studies on Complement Fixation with Strains of Typhoid, Paratyphoid and Allied Organisms, Ztschr. f. Immunitätsforsch. u. exper. Therap., 1911, **11,** 58.

nished by the pooled serums of at least two guinea-pigs, and was employed in a dosage of 0.05 c.c. of a dilution of 1 to 4 in salt solution. The red corpuscles were used in a 1 per cent. suspension.

A preliminary test was made of the hemolytic system, using 0.05 c.c. of complement and 0.5 c.c. of a 1 per cent. suspension of fresh sheep cells. In the titration of the antigen, as well as for the actual complement fixation tests, two hemolytic units (about 0.2 to 0.1 c.c. of a dilution of 1 to 100 in saline) were employed.

Preliminary tests were made to rule out any anticomplementary activity of the different antigens used. These were carried out as follows:

To each series of tubes containing decreasing doses (from 0.8 to 0.7 c.c.) of antigen diluted with 1.5 c.c. of salt solution was added 0.05 c.c. of complement in a dilution of 1 to 4. The tubes were incubated at 37 C. in a water-bath. To each tube was then added a previously prepared mixture of two units of hemolysin and 0.5 c.c. of the corpuscle suspension. After mixing and incubating for one hour, sedimentation of the red cells was hastened by placing the tubes in the refrigerator so as to make the readings more specific. In using a 1 per cent. suspension, very clear results are obtained, which make possible a quantitative expression of the degrees of fixation.

The actual tests with the three antigens were carried out in the following manner: To each 0.1 c.c. of serum was added 0.05 c.c. of complement in 1.5 c.c. of salt solution, followed by decreasing amounts of antigen. After incubation for a period of one-half hour the sensitized corpuscle suspension was added to each tube in the dosage already given. The mixture was then re-incubated for from one to two hours and the readings made already indicated.

The customary controls for the serums, antigen, hemolytic system were employed in duplicate at the beginning and at the end of each series.

On previous ocasions we made the observation that human serums may show, in a few instances, nonspecific fixation in dilutions of 0.2 c.c. with broth antigens. To rule out such nonspecific reactions we made use of *B. coli* antigen, and all the serums which gave fixation with this antigen, even when 50 per cent. hemolysis was noted, are regarded as nonspecific. Several serums of women were anticomplementary in double or single amounts (from 0.2 c.c. to 0.1 c.c.); these are mentioned, therefore, in a separate column. The range of specific fixation is considerable with broth antigens in comparison with extracts or suspensions and is, in part, responsible for the number of reactions recorded. In doubtful cases we tested the serums also with extract antigens, and the results confirmed those noted with our regular preparations.

The three complement fixation tests on ninety-eight persons are summarized in Table 2. These include the subjects tested for agglutinins, and also six others from whom insufficient blood was obtained for both experiments. The cases are again divided, according to their previous history, into five main groups.

TABLE 2.—Percentage of Complement Fixation Reactions

Group	Vaccine Preparation	Time Interval	Amount of Antigen Fixed by 0.1 C.c. Serum				Anticomplementary or Autotropic Serum	No. Cases
			0.2	0.1	0.05	0.02		
1	Army vaccine, first time....	8 mo.	45.4	27.2	27.2	.....	.....	11
	Army vaccine, first time....	2 mo.	100	100	50	50	.....	2
	Army vaccine, repeated inoculations	8 mo.	69.2	30.7	15.3	.....	(15.3)	13
2	Gay-Claypole sensitized vaccine sediment, first time	7 to 10 mo.	13.3	13.3	.....	.....	(20)	15
	Gay-Claypole sensitized vaccine sediment, first time	2 mo.	66.6	.....	.....	.....	(33.3)	3
	Gay-Claypole sensitized vaccine sediment, repeated inoculations	8 mo.	52.9	23.5	17.6	.....	.....	17
	Gay-Claypole sensitized vaccine sediment, repeated inoculations	6 mo.	.....	.....	.....	.....	.....	1
	Gay-Claypole sensitized vaccine sediment, repeated inoculations	2 mo.	100	100	100	.....	.....	1
3	Negative history.....	.....	5.5	.....	.....	.....	(16.6)	18
4	Typhoid fever.....	3½ to 25 yr.	10	10	.....	.....	(10)	10
5	Typhoid fever and vaccinated with army vaccine	6 to 8 mo.	80	40	40	.....	.....	5
	Typhoid fever and vaccinated with Gay-Claypole vaccine	6 to 8 mo.	50	50	.....	.....	.....	2

The first group comprises twenty-six persons who had been vaccinated with army vaccine three to eight months previous to the tests. Thirteen of these were immunized for the first time, and the same number had had repeated inoculations with either army or sensitized vaccine. In this group a fairly high percentage, about 45.5 per cent., furnished serums which even in amounts of 0.1 c.c. fixed the specific antigen in quantities of 0.2 c.c. Detailed records of the test indicate that the army strain gives somewhat better fixation than the polyvalent

antigen; and, in the light of the recent findings of Hooker,[41] the discussion of Garbat[42] that the *B. typhosus* strain "Rawlings" differs immunologically from many recently isolated strains of typhoid organisms, this observation is readily explained. Only about 27.2 per cent. of the serums contained large amounts of fixing antibodies, most of them giving reactions only with the largest amount of antigen used in the tests. In two serums derived from individuals who had been vaccinated three months previous to the test the complement fixing antibodies were still high, and in one sample even higher than the agglutinins (1 to 80). It is quite apparent that the fixing antibodies disappear just as irregularly as was noted for the agglutinins. The length of time during which they remain in the serum is difficult to determine without repeated tests on the same subjects; but one may be certain at least that they persist in some persons, vaccinated for the first time, for longer periods than has been usually supposed. In this connection Hage and Korff-Petersen[2] recently reported, using an extract antigen, that some persons may give fixation with from 0.01 to 0.025 c.c. antigen five to nine months after an initial antityphoid vaccination.

Repeated vaccination apparently favors this persistence of the complement fixing antibodies, inasmuch as nearly 70 per cent. of the thirteen cases in Group 1 still gave slight fixation of the complement. Unfortunately, the serums of two cases in this group were anticomplementary. The degree of fixation, however, was slight, only the maximum amount of antigen having been absorbed by the serum. In some instances a parallelism between the degree of fixation and the agglutination was evident, but no definite relationship could be established.

The conclusions from experimental work on animals that the complement fixing antibodies, which ordinarily develop later than the agglutinins in the blood serum, remain longer demonstrable are apparently not applicable to man. It would appear that the degree and persistence of these immune bodies is as irregular and as inconstant as was noted in the case of the agglutinins.

In the second group, containing thirty-seven subjects vaccinated with Gay-Claypole vaccine sediment, eighteen had received the sensitized vaccine sediment for the first time. The serums of those inoculated from seven to ten months previously showed, in 13.3 per cent. of the cases, fixation of the complement; the degree of the reaction

41. Hooker, Sanford B.: Preliminary Studies on the Antigenic Properties of Different Strains of Bacillus Typhosus, Proc. Soc. Exper. Biol. and Med., 1916, **13,** 139.

42. Garbat, A. L.: Studies in Typhoid Fever. Reference to a paper read before the American Association of Immunologists, Jour. Am. Med. Assn., 1916, **67,** 149.

was less marked than in Group 1. It is possible, however, that an additional 20 per cent. of serums can be added to the 13.3 per cent. which were not counted as positive on account of the anticomplementary action of the double or single serum controls. The total of 43.3 per cent. for fifteen serums would fairly correspond with the result obtained in Group 1.

We are at present unable to explain the high percentage of autotropic or anticomplementary serums in this group of subjects inoculated with sensitized vaccine. In so small a series they may, of course, be chance occurrences. Unfortunately, repeated tests were not possible, and prolonged exposure to higher temperature did not materially affect the serums. When reading Löwy's article several months after the tests were completed, we noted that he had already observed an analagous condition of the serums in rabbits vaccinated with sensitized living organisms. A separate experimental study, undertaken quite recently by one of use (K. F. M.) to explain the phenomenon, is now in progress.

The serums of three patients vaccinated two months ago still gave fixation with the polyvalent as well as with army antigen. As a rule, the serums of Group 2 gave just as good fixation with the polyvalent antigen as with the army and the extract antigens. Slight differences were noted, in two cases only, in the amounts of antigen bound by 0.1 c.c. of serum.

In nineteen subjects who had been repeatedly vaccinated with sensitized or army vaccine, about 50 per cent. of the serums gave positive complement fixation reactions. This series of cases supports the view already expressed that repeated vaccinations favor the persistence of fixing substances. To what extent the previous army vaccination had influenced the reactions in Group 2 is, of course, a matter of speculation.

Only a few points in connection with Group 3 need explanation. Of eighteen subjects with negative histories, one gave a decided complement fixation reaction and a marked agglutination. This case was therefore considered, as previously stated, a probable instance of unrecognized typhoid fever. The remaining seventeen serums gave complete hemolysis with the various antigens. Two of these (both from women) showed delayed hemolysis in the serum controls and with *B. coli* antigens.

Among ten subjects in Group 4, who had a definite history of typhoid fever, complement fixation was present in but one case, a woman who had had typhoid fever three and one-half years before. In another case a delayed hemolysis with four different antigens was observed on several occasions, when blood was collected for other

purposes. Our findings, therefore, are quite in accord with those reported in the literature.

Of seven subjects (Group 5) who, in addition to having had typhoid fever, had been vaccinated from six to eight months previous to the serum tests, five gave positive complement fixation reactions. One of them, who in January gave a fixation with 0.2 c.c., gave in June of the same year, with three entirely different antigens and five different serum samples collected from one to six days apart, the same or even better fixation. In this individual the agglutinins were still high.

Unlike the agglutinins, the difference between the percentages of complement fixation reaction following inoculations with army vaccine as compared with sensitized vaccine sediment is relatively small; and it is easily possible that in another series the relations would be reversed. Indeed, in rabbits Nègre and Löwy reported greater production of complement fixing antibodies from injections of living sensitized vaccine than from unsensitized heat or ether killed vaccines (Wright's or Vincent's). Ardin-Delteil, Nègre and Raynaud obtained similar results with human beings. Very little is known, however, about the immune substances (bactericidal and complement fixing antibodies) called forth by sensitized vaccine sediment. According to von Liebermann, Theobald Smith and others, there is serious doubt that any of the sensitized vaccines as prepared at the present time have any uniformity in antigenic power. Moreover, in the case of the sensitized vaccine sediment of Gay and Claypole it is possible that the chemical and mechanical destruction and subsequent extraction of the residue will further influence its antigenic properties.

The chart, it will be seen, strongly suggests that repeated vaccinations favor the persistence of complement fixing bodies.

THE RELATION OF THE AGGLUTININS AND COMPLEMENT FIXING ANTIBODIES TO THE TYPHOIDIN QUOTIENT

Elsewhere in this number of this journal it is shown by one of us that the typhoidin cutaneous test as measured by the typhoidin quotient, while it bears some relation to immunity, is exceedingly variable in its results. The subjects of these serologic experiments were the same as those for the series of typhoidin tests, the blood being drawn in each case at the time of performing the typhoidin inoculation. In Table 3 the average typhoidin quotients are compared with the agglutinin and complement fixing antibody averages in the five groups of subjects.

Inspection of this table shows a certain amount of relationship between the serologic findings and the typhoidin quotients. In all three columns there are low averages in the "negative history" group

and higher ones among the groups of supposedly typhoid immunes. The correspondence is far from exact, however, as is inevitable in a series of this size in which the figures of each group vary so much among themselves and in which the differences between the group averages, particularly among the typhoidin quotients, are not great. So that little can be said from the comparison other than that some relationship exists between all three tests and the typhoid experience of the subjects.

TABLE 3.—COMPARISON OF SERUM REACTIONS WITH TYPHOIDIN REACTION

Group	Number of Cases	Method of Vaccination	Time Interval	Average Agglutination Titration	Percentage of Complement Fixation	Average Typhoidin Quotient
1	12 A.*(12 C.F.)	Army vaccine, first time...	3 to 8 mo.	1:148	53.8	1.46
	11 A. (12 C.F.)	Army vaccine, repeated....	8 mo.	1:20	69	1.42
2	17 A. (18 C.F.)	Gay-Claypole sensitized sediment	2 to 10 mo.	1:22	44	1.4
	17 A. (19 C.F.)	Gay-Claypole sensitized sediment, repeated	2 to 8 mo.	1:59	47	1.48
3	18	Negative history.....	.....	1:20	5.5	1.4
4	10	Typhoid fever.....	3½ to 25 yr.	1:28	10	1.42
5	7	Typhoid fever and vaccinated	6 to 8 mo. before	1:59	71.4	1.56

* The letter A. signifies agglutination; C.F., complement fixation.

COMMENT

Hesitation has just been expressed in stating any very definite relationship between complement fixation, agglutination and the typhoidin cutaneous test. Still greater caution needs to be exercised before interpreting the findings of any of these procedures in terms of immunity. It should be clearly recognized that the only reason for attaching an immunity significance to one of these tests is the fact that they are positive (part of the time and in varying degrees) among classes of individuals who, experience has proved, are largely (not invariably) immune to typhoid fever. It has never been shown that the cases of typhoid fever subsequent to vaccination or a previous attack of the disease are those who react negatively to any of these tests. Moreover the low averages in all three columns of Table 3 (those who have had typhoid fever), if substantiated by sufficient

numbers of observations, would have to be regarded as distinctly limiting the value of these tests as indexes of immunity; because it is well known that most of those who have had typhoid fever even many years ago are highly immune.[20] There is nothing in our results, therefore, which is not in harmony with the long-accepted idea that the estimation of antibodies furnishes no accurate index of the power which the body possesses of defending itself against invasion by typhoid organisms. Thus, Garbat and Meyer[43] found that serums of rabbits immunized with sensitized cultures were highly protective (more so than animals treated with nonsensitized preparations), and yet this potent serum contained but small amounts of agglutinins and complement fixing antibodies.

We were unfortunately unable to carry out bacteriolytic experiments with the quantities of serum at our disposal. Neufeld and Hüne[44] found no definite relation between the complement deviating properties of the typhoid immune serum and the content of bacteriolytic amboceptors. But according to Wollstein[8] and Howell[4] the bactericidal properties of serums of persons immunized with Russell's vaccine behave in many respects similar to the complement fixing antibodies in our tests.

It is clear that too little is known about the serologic or cutaneous tests as indexes of typhoid immunity at the present time to make them worth anything when applied to individual cases with the idea of deciding about the need for prophylactic inoculation. Neither can they in their present development form the basis of reliable statistical researches to determine the relative merits of different types of vaccines. From the reviews of the literature, it is also evident that for further advances in the subject we must look to carefully controlled experiments with large numbers of observations. Our own series, while it is larger than the majority of those reported in the recent literature, and furnishes fairly definite information and suggestions on certain points, is too small to throw any light on some of the important questions involved.

CONCLUSIONS

Agglutination and complement fixation reactions have been studied in ninety-eight healthy individuals. Some of the subgroups are too small to warrant final conclusions, but the following points have a fair degree of probability:

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43. Garbat and Meyer: Ueber Typhus Heilserum, Ztschr. f. exper. Path. u. Therap., 1910, **8**, 1.

44. Neufeld, F., and Hüne: Untersuchungen über bactericide Immunität und Phagocytose nebst Beiträgen zur Komplementablenkung, Arb. a. d. k. Gsndhtsamte., 1907, **25**, 201.

1. In comparison with army vaccine, sensitized vaccine sediment produces small amounts of agglutinins.

2. Complement fixing antibodies are found in about equal amounts in the serum of those who have had army vaccine and those who have received sensitized vaccine.

3. It has been shown anew that for individual cases serologic and allergic immunity tests in their present form are inconclusive as measures of typhoid immunity.

45. In addition to the references already given, the following will be found of interest:

Garbat, A. L.: The Complement Fixation Test in Typhoid Fever, Its Comparison with the Agglutination and Blood Culture Method, Am. Jour. Med. Sc., 1914, **148,** 84.

Kilgore, Eugene S.: The Typhoidin Quotient, THE ARCHIVES INT. MED., 1916, **17,** 25.

Liebermann, L., and Acél, D.: Ueber antigene Wirkung sensibilisierter und nicht sensibilisierter Blutzellen und Typhusbacterien, Deutsch. med. Wchnschr., 1915, **41,** 965.

Smith, T.: The Underlying Problems of Immunization; reference in Jour. Am. Med. Assn., 1916, **66,** 1740, and Med. Rec., New York, 1916, **89,** 974.

Ardin-Delteil, Nègre and Raynaud: Recherches cliniques et experimentales sur la vaccinotherapie de la fievre typhoide par le virus sensibilise de Besredka, Ann. de l'Inst. Pasteur, 1913, **27,** 644.

Force, J. N.: Institutional Vaccination Against Typhoid Fever, Am. Jour. Pub. Health, 1913, **3,** 750.

d-GLUCOSE TOLERANCE IN HEALTH AND DISEASE*

RUSSELL M. WILDER, M.D., AND W. D. SANSUM, M.D.
CHICAGO

In previous communications[1] from this laboratory descriptions have been given of apparatus devised for the purpose of making continuous intravenous injections at accurately controlled rates. The present paper deals with the application of this apparatus and the principles of timed intravenous injection to a clinical study of glucose tolerance in normal human individuals and in a series of pathologic conditions. In order that the work may appear in its proper relationship to that of previous writers the more important contributions to the subject may be reviewed.

It has long been known that sugars administered by mouth in sufficient amounts cause melituria, but an attempt to learn the size of the dose which would accomplish this was first made by Worm Müller[2] in 1884. Two healthy men on a diet free from carbohydrate received weighed quantities of glucose, lactose and saccharose and it was found that 50 gm. of glucose, 50 gm. of saccharose or 100 gm. of lactose produced just a trace of reducing substance in the urine, while larger doses caused severe melituria.

Hofmeister[3] in 1889 conducted a more elaborate investigation with dogs. The sugar was fed by mouth and it was found that the maximum dose that could be given and just fail to cause sugar to appear in the urine was very constant for the individual dog, although widely different for different dogs. This dose he called the "assimilation limit," a term that has since been widely employed. Hofmeister is also the author of the term "tolerance," as applied to sugars, which he used in the following connection:[4]

> The diabetic of the milder type on a strictly regulated meat diet has a certain tolerance for sugars and starches, inasmuch as he only passes a saccharine urine when such substances are administered in excess of a definite limit.

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* Submitted for publication Aug. 11, 1916.

* From the Otho S. A. Sprague Memorial Institute Laboratory for Clinical Research, Rush Medical College, and the Medical Clinic of the Presbyterian Hospital, Chicago.

1. Woodyatt, Sansum and Wilder: Jour. Am. Med. Assn., 1915, **65**, 2067.
2. Müller, Worm: Arch. f. d. ges. Physiol., 1884, **34**, 576.
3. Hofmeister: Arch. f. exper. Path. u. Pharmakol., 1889, **25**, 240.
4. Der Diabetiker, leichterer Form zeigt, bei streng gehandhabter Fleischkost, eine gewisse Toleranz für Zucker und für Amylacien, insofern er nur bei Zufuhr derselben über eine gewisse Grenze hinaus Zuckerhaltigen Harn liefert.

It does not appear that he drew a distinction between tolerance and assimilation limits, and since this time assimilation limits, as measured by Hofmeister's method, have been interpreted as tolerance limits.

In 1895 Linossier and Roque[5] confirmed the observations of Worm Müller and Hofmeister, but proposed, as a truer measure of the assimilability (Nutzwert) of a sugar, the coefficient obtained by dividing the quantity of sugar excreted by the quantity given. The constants as found by these authors were variable, even for the same sugar; but in 1898 Gilbert and Carnot[6] obtained a fairly constant ratio of excretion to administration by giving the sugar intravenously. Inconstant proportions occurred when the injected amounts were small, but with doses between 2.5 and 10 gm. per kilogram of body weight, the ratio of grams excreted and grams injected was always about 40 to 100.

The intravenous injection of sugar is an old procedure and it has frequently been observed when different sugars were given in this way that some were excreted more freely than others. On the basis of such observations conclusions have been drawn regarding the relative utilizabilities of the various sugars. But whether these conclusions are justified on the basis of the experiments made is open to question because of the excessive variations that occur in the results of different writers and even in those of the same observer. Pavy,[7] for example, after injecting the same sugar (glucose) in doses of 0.25 gm. per kilogram of body weight in a series of rabbits, recovered in the urine of one as little as 3.1 per cent. and from another as much as 39.6 per cent. More consistent results with intravenous injections were obtained by McGuigan and Mathews,[8] who gave dilute, 0.5 per cent., sugar solution in such a manner that 5 c.c. entered every five minutes. In some cases these injections were continued for as long as seventy-seven minutes and conclusions concerning the relative ease of oxidation of the sugars were drawn from their time of appearance in the urine. Previous to this Doyon and Dufourt[9] had discovered that the *rate* of intravenous administration influenced the amount of sugar excreted and it would appear that the variation in the results obtained by the earlier writers was due to their failure to appreciate the importance of controlling the rate of injection. Doyon and Dufourt used dogs and gave to each 2 gm. of glucose per kilogram of body weight, "en un temps variable mais avec une vitesse toujours uniforme." They do not explain how they maintained such constant injection rates and simply report the

5. Linossier and Roque: Arch. de méd. expér. et d'anat. path., 1895, **7,** 228.
6. Gilbert and Carnot: Compt. rend. Soc. de biol., 1898, **50,** 330.
7. Pavy: Jour. Physiol., 1899, **24,** 479.
8. McGuigan and Mathews: Am. Jour. Physiol., 1907, **19,** 175.
9. Doyon and Dufourt: Jour. de physiol. expér., 1901, **3,** 703.

result of one typical experiment which disclosed that 98.64 per cent. of the sugar was retained if the duration of the injection was made eighty minutes, while only 85.62 per cent. remained in the body when the same quantity was injected in fifteen minutes.

In 1905 Blumenthal[10] pointed out that the utilization of sugar by the tissues is expressible only in terms that apply to velocities, for example, as unit weight of sugar, per unit weight of tissue, per unit weight of time. The rate at which sugar is brought to the tissues must therefore be controlled if it is desired to measure its rate of utilization. This necessitates precise knowledge of the rate at which it enters the blood; but when a sugar is given by any method entailing absorption as a preliminary to its entrance into the blood, the latter rate is subject to uncontrollable variations. The most nearly exact method of determining sugar tolerance must therefore consist in direct intravenous injection. These principles he applied in a series of experiments and found (1) that glucose could be rapidly injected into rabbits in doses of about 0.85 gm. per kilogram of body weight without causing melituria, but if this dose was only slightly exceeded or if within a short time after the first dose a second injection was made, intense melituria would result; (2) that a dose of sugar could be selected which could be repeatedly injected at fifteen minute intervals for indefinite periods and always just fail to appear in the urine. From these observations Blumenthal concluded that the tissues are able to remove sugar from the blood at a rapid rate up to a certain limit, that is, until they have become "saturated," but no inference concerning utilization can be drawn from the size of the dose necessary to cause saturation or the rate at which this dose is absorbed. Such a dose represents simply a saturation limit (*Sättigungsgrenze*). On the other hand, that dose whose repeated injection at fifteen minute intervals just fails to produce melituria gives a measure of utilization, a utilization limit (*Ausnutzungsgrenze*). For glucose in rabbits this was found to be between 0.15 and 0.325 gm. per kilogram of body weight per fifteen minutes, that is, from 0.6 to 1.2 gm. per kilogram per hour.

In 1906 Comessatti[11] used the Blumenthal method and demonstrated that sugar assimilation was increased by exercise. During rest, doses of 0.2 gm. per kilogram per fifteen minutes led to melituria in two rabbits, while after exercise in a treadmill doses of 0.25 gm. given in the same manner caused no glycosuria. In 1909 Loeb and Staddler,[12] with the same method, obtained figures in resting rabbits which were lower than those reported by Blumenthal (0.09 and 0.16

10. Blumenthal: Beitr. z. chem. Phys. u. Path., 1905, **6,** 329.
11. Comessatti: Beitr. z. chem. Physiol. u. Path., 1906, **9,** 67.
12. Loeb and Staddler: Arch. f. exper. Path. u. Pharmakol., 1914, **77,** 326.

gm. per kilogram of body weight per fifteen minutes, that is 0.36 and 0.64 gm. per kilogram per hour).

There can be no doubt of the correctness of the principle stated by Blumenthal or of the insuperable difficulties which lie in the way of accurate measurement of the power of the tissues to utilize sugar when methods are used in which it is impossible to control the rate of entry of sugar into the blood. If the sugar is given by mouth, as in the Hofmeister procedure, the rate of absorption will depend on variable factors entirely beyond control, and when the subcutaneous or intraperitoneal routes are chosen the same difficulty is encountered. A tolerance limit obtained by such methods is at best only the resultant of absorption and utilization, and yet since the appearance of Blumenthal's article writers other than those quoted above have failed to appreciate the soundness of his views and continue in their adherence to absorption methods.

In clinical studies it is a common practice to give by mouth 100 gm. of d-glucose dissolved in 200 c.c. of water or lemonade and to speak of a low tolerance if this amount of sugar leads to melituria. If no melituria results when 150 or 200 gm. are fed, tolerance is considered high, but the test is by no means reliable, as many normal persons can tolerate any quantity of glucose which they can be made to take and retain, a fact which has been confirmed strikingly by the experiments of Taylor and Hutton.[13] Nevertheless, such tests have been applied in a wide variety of clinical conditions, especially in diseases of the "glands of internal secretion," and have formed the basis of extensive theory. Other methods for measuring tolerance have received little attention from clinicians. Subcutaneous injections of sugar have been made (Voit,[14] Achard[15] and others), but the pain and danger of infections which they involve have limited their general use. Intravenous sugar injections, while employed for therapeutic purposes (Kausch[16] and others) have not been used in clinical tolerance studies and the attention of clinicians seems not to have been directed to the contribution of Blumenthal.

But while Blumenthal's statement of the principles governing accurate measurement of sugar tolerance is sound and demands recognition, his technical application of these principles is capable of improvement. This is particularly true if the method is to be applied in clinical investigation. Blumenthal's method involves repeated injections at fifteen minute intervals, and the technical difficulties of performing these on time, and with assurance that no leakage occurs, are

13. Taylor and Hutton: Jour. Biol. Chem., 1916, **25,** 173.
14. Voit, F.: Deutsch. Arch. f. klin. Med., 1897, **58,** 523.
15. Achard, cited by Lepine: Le diabète sucré, Paris, 1909, p. 234.
16. Kausch: Deutsch. med. Wchnschr., 1911, **37,** 8.

very material, particularly in patients with small superficial veins. The Blumenthal procedure is furthermore insufficient to accomplish that which Blumenthal's principles demand, namely, a perfect control of the rate of administration. His injections, repeated every fifteen minutes, are not continued at a uniform rate over the fifteen minutes, but are given rapidly at the beginning of each period. Under these conditions it is clear that in the first part of each fifteen minute period, that is, during the time actually occupied by the injection, the concentration of sugar in the blood must rise as a wave and in the interval between the injections the concentration must fall. If now the injection is made more rapidly in one case than another, the crest of the wave produced will be higher, and such a wave may overflow the kidney threshold and result in melituria, even though the tolerance for the fifteen minute period is by no means exceeded. Under these conditions it is incorrect to assume that a melituria indicates that the rate of utilization for the period has been overstepped. That this objection to Blumenthal's procedure is sound is shown by figures for the tolerance of rabbits published by Blumenthal,[10] by Comessatti[11] and by Loeb and Staddler,[12] all of whom used the same method. One rabbit of Blumenthal's showed a tolerance of 0.325 gm. per kilogram of body weight per fifteen minute period, while one of Loeb and Staddler's was as low as 0.09 gm. per kilogram per fifteen minutes; and Blumenthal's own results ranged, as stated above, from 0.15 to 0.325 gm. per kilogram per fifteen minutes, a variation of over 100 per cent. It is probable that the higher figures obtained by these authors were more nearly correct than the lower ones and that the latter occurred when the injections were made too rapidly.

In order to avoid periodic waves of sugar concentration and to give no opportunity for melituria to occur until the rate of administration at all times surpasses that of utilization, it is clearly advisable to discard intermittent or discontinuous injections in favor of continuous administration at constant rates. The latter procedure was adopted in the present study, and for the purpose of giving continuous injections use was made of the apparatus referred to above. This apparatus consists of a small pump which is driven by an electric motor. The stroke of the pump may be made very short and the number of strokes per minute raised to forty or sixty, so that the stream pumped is practically continuous. Such pulsations as occur are furthermore almost obliterated by the elasticity of the rubber tubing that connects the pump with the needle in the patient's vein. The rates of injection are easily controlled and accurately regulated by means of a rheostat.

By the use of this instrument it is a simple matter to find that rate of injection which just equals the rate of utilization or the tolerance limit.

The limits for d-glucose of different dogs and rabbits tested in this way were nearly constant and approximated Blumenthal's higher figures, as might be anticipated. Reports of these animal experiments will appear in other communications, as the present paper is limited to the results obtained in human subjects.

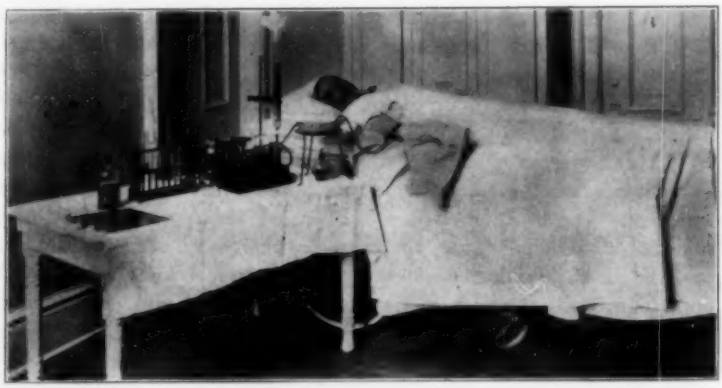
PROCEDURE IN TESTING THE d-GLUCOSE TOLERANCE OF MAN

It is to be anticipated that the intravenous tolerance limits for glucose will vary with a number of physiologic factors capable of influencing the basal metabolism. If the tolerance is expressed as grams of glucose per unit of body weight per unit of time, then sex, age, the proportion of the different types of tissue entering the body structure, the relative proportion of fat, glycogen and protein in the respective tissues, the ratio of surface to mass, the state of the activity of the muscles, etc., all require due consideration. In the present study it was found that in health both men and women showed the same tolerance. The influence of age was minimized by confining the work to adults between the ages of 20 and 45. (One child of 14 is reported.) The subjects chosen were with one exception in an average state of nutrition. All had been on a general mixed diet for several days before examination and none had partaken excessively of carbohydrates. On the day of the test no food was given by mouth and the sugar injection was commenced in the afternoon between 2 and 4 p. m. Uniform conditions of rest were secured by keeping the subjects in bed on the day of the test, and finally, in order to minimize possible delays in the excretion of glucose, once the tolerance limit had been exceeded, as well as to study the effects of different rates of glucose injection on the diuresis, water was given by mouth in amounts equivalent to the amount of fluid necessary to administer during the injection, in such a way that the subject would receive during each hour of the foreperiod an amount of water equivalent to the quantity which he was to receive by vein in each hour of the test.

Material.—The d-glucose employed in earlier experiments was a preparation of Merck labeled "purissimum." Later a high grade granular commercial dextrose (Argo corn sugar) was purified in the laboratory by decoloration with animal charcoal and repeated recrystallization from alcohol. The final product was dissolved in freshly distilled water (prepared with such precautions as are employed for salvarsan administration) to make from 16 to 20 per cent. solutions. (The molecular weight of glucose being 180, the gram molecular solution is 18 per cent.) Such a solution is sufficiently hypertonic to avoid hemolysis and has been found for other reasons to be the best standard solution to employ for the present purposes. In earlier experiments

solutions of greater strength were employed, with a view to keeping the volume injected small, but the opportunity for slight variations in the injection rate was thereby correspondingly increased and on this account the 18 per cent. solutions were adopted. The solutions showed only pale straw color when observed in flasks of two liter volume, smaller volumes appearing colorless. The solutions were divided in one and two liter flasks which were sterilized in the autoclave. The titer of each was determined by a polariscope directly before injection.

In the entire course of this work, in which the solutions were injected at rates slightly above and below the tolerance limit, no chills, shock or other general reactions were encountered. In two cases thrombosis of the vein used for the injection resulted. In one of these



Illustrating apparatus and method of making the glucose injection.

the thrombus was limited to an inch of the vein, in the other it extended to the axilla, but in neither did it result in a bad effect. It is probable that the thrombus formation in the most extensive of these cases was favored by trauma, as the subject of the test refereed a football game on the day after his injection.

Technic of Injection.—As previously stated, use is made of the injecting machine developed in this laboratory and described elsewhere. A buret to serve as a reservoir, together with the necessary rubber tubing, are sterilized by autoclave. The parts of the pump which come into contact with the fluid are removed and boiled. The apparatus is then assembled in the manner illustrated, the glucose solution is poured into the buret and all air expelled from the tube and pump.

The initial rate for injection is purposely chosen below what is thought to be the velocity of assimilation; for example, if the subject is apparently normal, it is assumed that a rate of 0.7 gm. per kilogram of body weight per hour will be tolerated, and this rate is given. If the patient weighs 75 kg. and the glucose solution, as determined by polariscope, is 20 per cent., this would mean an injection of $0.7 \times 75 \times 5$, or 262.5 c.c. of a 20 per cent. solution per hour, or 4.37 c.c. per minute. The machine is set to deliver the solution at this rate, the needle is introduced into a suitable vein and the injection begins.

This initial injection rate must be maintained long enough to permit a thorough saturation of the tissues before the urine is collected and tested for sugar. This requires from twenty to thirty minutes, as has been found by experiment. If the injection rate only slightly exceeds the rate of utilization, glycosuria will occur within this time; if it does not, no glycosuria will occur even after several hours of continuous injection. This latter statement is based on experiments with dogs. For this reason the first collection of urine is made about thirty minutes after the beginning of the experiment. One cubic centimeter of urine is added to 5 c.c. of heated Haines' solution, the mixture boiled for ten seconds and cooled and the absence of reduction is taken to indicate that the tolerance of the patient lies above the rate of injection. The injection is then accelerated and continued for thirty minutes at this higher rate, for example, at 0.8 gm. per kilogram per hour in the case under consideration. The urine is then tested again and by gradually stepping up the rate of injection, 0.1 gm. per kilogram per hour at a time, that rate can be found which first causes glycosuria and the rate just preceding this is accepted as the tolerance limit.

RESULTS

d-Glucose Tolerance in Health.—Four young adults, two men and two women, were chosen for the tests of normal glucose tolerance. All of them had been working in the medical college or the hospital and were known to be in good health. On the day preceding the test they were put to bed and subjected to the experimental conditions outlined above. The results in all these cases were the same. Glucose injected at the rate of 0.8 gm. per kilogram of body weight per hour caused no glycosuria, but in each case sugar appeared in the urine when the injection rate was 0.9 gm. per kilogram per hour. From this it would appear that the tolerance limit for d-glucose of normal men and women is practically constant and that it equals a rate of approximately 0.85 gm. per kilogram of body weight per hour of time. For a 75 kg. man such an injection would represent the administration of 63.75 gm. per hour.

Tolerance in Diseases of the Pancreas.—Three patients, one with organic disease of the pancreas and the other two with suspected mild diabetes mellitus, were tested for their glucose tolerance. In both a low limit was demonstrable. The first suffered from a chronic interstitial pancreatitis, a diagnosis which was confirmed by subsequent operation. His tolerance limit lay below 0.7 gm. per kilogram of body weight per hour. The second patient had recently shown a trace of sugar in the urine at a life insurance examination, but had been sugar free since then. His tolerance lay below 0.5 gm. per kilogram per hour. The third was similar to the second, with a tolerance of 0.4 gm. per kilogram per hour; but since the state of his nutrition and other factors besides the pancreatic disease were not strictly comparable with the controls, some reserve is expressed as to the significance of this result.

Tolerance in Diseases of the Thyroid.—Five patients with exophthalmic goiter, two men and three women, have been tested for their glucose assimilation and in all the tolerance limits were reduced. Two of these patients had severe general symptoms and these cases showed glycosuria when glucose was administered at the rate of 0.5 gm. per kilogram per hour. Two milder cases gave a limit exceeded by the administration of 0.6 gm. per kilogram per hour, and the fifth, a still milder case, had a tolerance between 0.6 and 0.7 gm. per kilogram per hour. It would appear, therefore, that a depressed glucose tolerance is a fairly constant accompaniment of exophthalmic goiter. Such results are in harmony with the observation of alimentary glycosuria in exophthalmic goiter made by Kraus and Ludwig,[17] Chvostek,[18] Falta[19] and many others and with the glycosurias which may be produced in animals and normal persons by feeding thyroid tablets (Ewald,[20] Dale,[21] Denning,[22] von Noorden[23] and others). On the other hand, a typical case of myxedema was found to have a normal tolerance, by the intravenous method, a result which is not in agreement with the observations of those who use the alimentary tests and find high assimilation limits in this disease, suggesting that a delay in the rate of absorption is accountable for their findings.

Tolerance in Disease of the Hypophysis.—Two cases of acromegaly have been studied, one case of suspected gigantism and two with dys-

17. Kraus and Ludwig: Wien. klin. Wchnschr., 1891, **4,** 898.
18. Chvostek: Wien. klin. Wchnschr., 1892, **5,** 17.
19. Falta: Die Erkrankungen der Blutdrüsen, Berlin, 1913, p. 65.
20. Ewald: Die Erkrankungen der Schilddrüsen, Myxödem und Kretinismus, Ed. 2, Leipzig, 1909.
21. Dale: Brit. Jour. Dermat., 1894, **6,** 177.
22. Denning: München. med. Wchnschr., 1895, **42,** 389.
23. Von Noorden: Ueber den Einfluss der Schilddrüsenbehandlung auf den Kohlehydratstoffwechsel, Berl. klin. Wchnschr., 1897, **34,** 518.

pituitarism, showing the Fröhlich syndrome. The glucose tolerance of all these cases was found to lie close to the normal limits. Three showed a bare trace of sugar in the urine after the injection of 0.8 gm. per kilogram per hour and all gave a definite glycosuria after receiving 0.9 gm. per kilogram per hour. These results are in disagreement with those obtained when the oral administration is used (Cushing,[24] Bondi,[25] Falta[19]) and suggest, as in the case of myxedema, that the increased tolerance of such patients for sugar given by mouth is due rather to a retarded absorption from the bowel than to any anomaly of the intermediate metabolism, as certain writers have assumed.

Tolerance in Cirrhosis of the Liver.—A normal d-glucose tolerance limit was found in a case of alcoholic cirrhosis.

SUMMARY

Adopting the premise previously suggested by Doyon and Dufourt, and notably Blumenthal, that glucose tolerance must be dealt with as a velocity, that is, in terms of the number of grams of glucose which may be brought into the tissue per unit of body weight per unit of time without causing an abnormal overflow of glucose into the urine, we injected from 16 to 20 per cent. solutions of pure d-glucose intravenously at different uniform rates by means of the motor driven quantitative injection pump, which has been described in other reports from this laboratory. Observations have been made on rabbits, dogs, and normal resting men and women of average size, weight and nutrition. These experiments indicate that glycosuria appears when the rate of injection lies above 0.8 gm. and below 0.9 gm. per kilogram of body weight per hour.

It is realized that variations from these limits may be ascribed, *a priori*, to any one of several factors, namely, (1) variation in the ability of the colloids of the body at large, including those of the kidney, to hold glucose in a state of adsorption or its equivalent (variations in the threshold for glucose); (2) the variation in the rate at which glucose may be entering the cells from endogenous sources, notably glycogen and protein, but especially the former, since endogenous supplies of glucose to the cells must be regarded as superadding themselves to the glucose supplied by injection; (3) to variation in the rate at which glucose can be utilized within the cell, the utilization in this instance being taken to imply the sum of those processes by which glucose may undergo a chemical change into some substance other than glucose.

The purpose of the present report is to record objectively experi-

24. Cushing: The Pituitary Body and Its Disorders, Philadelphia, 1911.
25. Bondi: Arch. f. exper. Path. u. Pharmakol., 1910, **63**, 347.

mental findings without entering into detailed considerations of the physiologic factors which have been concerned.

Observations have been made of the intravenous glucose tolerance limit in the following clinical conditions: chronic interstitial pancreatitis, one case; very mild diabetes, two cases; thyroid disease, six cases, five representing different grades of symptoms of hyperthyroidism and one a typical instance of myxedema; hypophysis disease, five cases giving clinical pictures which would be designated as such; gigantism (?), one case; Frölich syndrome, two cases (one with diabetes insipidus and one without); acromegaly two cases; and cirrhosis of the liver, one case.

Many questions which arise as to the variations of the intravenous glucose tolerance as the result of variations in the state of nutrition, the amount of stored glycogen, the character of the previous diet, the water and salt balance of the body, etc., will be further discussed in other reports from this laboratory.

CONCLUSIONS

The following conclusions would appear to be justified:

1. Normal resting adult men and women of average size, weight and nutrition begin to excrete abnormal quantities of glucose in the urine when the injection rate into the vein is above 0.8 gm. and below 0.9 gm. per kilogram of body weight per hour.

2. Cases of nondiabetic pancreas disease may evince a lowered tolerance for glucose when measured by this method even when administration of glucose by the alimentary route gives no definite evidence of such diminution. The same is true of very mild cases of diabetes mellitus. In these cases it may be fancied that the lowered tolerance arises from a diminished utilization.

3. Cases with increased thyroid function show a uniformly diminished intravenous glucose tolerance. In such cases it is suspected that this effect may be ascribed to an increased glycogenolysis, which is tantamount to an endogenous glucose supply to the cells superimposed on the intravenous injection, or, what amounts virtually to the same thing, a decreased ability on the part of the body to build up glycogen, since increased glycogenolysis implies the disbalance between the synthesis and catalysis of glycogen in favor of the latter. On the other hand, a case with decreased thyroid function (myxedema) showed no increased glucose tolerance, but appeared to have a normal tolerance, excreting sugar promptly when this was injected at a rate faster than 0.9 gm. per kilogram of body weight per hour.

4. In none of the cases of hypophysis disease has there been any increase of the glucose tolerance above the normal limits, but on the

contrary, a tendency toward decrease, which would seem to imply that increases of glucose tolerance in such cases, following alimentary administration of glucose, are due to delays in absorption rate rather than to changes in the intermediate metabolism.

5. The d-glucose tolerance of an advanced case of alcoholic cirrhosis of the liver was found to be normal.

6. The determination of glucose tolerance by the method described is a practical clinical procedure, more accurate than those methods which depend on absorption from a local site as a preliminary to the entrance of glucose into the blood and giving more constant results than have been obtained by any other technic involving intravenous injections.

PROTOCOLS AND CASE HISTORIES

The protocols of these experiments, the case records and a composite chart of the results (Fig. 2) are appended.

CASE 1.—B. T., a healthy woman, aged 25, weight 42.7 kg., rested in bed on the day of the test.

TABLE 1.—GLUCOSE SOLUTION, 18 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	3.16	30	0		
0.9	3.56	30	++	0.4	0.96
Subsequent loss					0.75+
Total glycosuria					1.71+

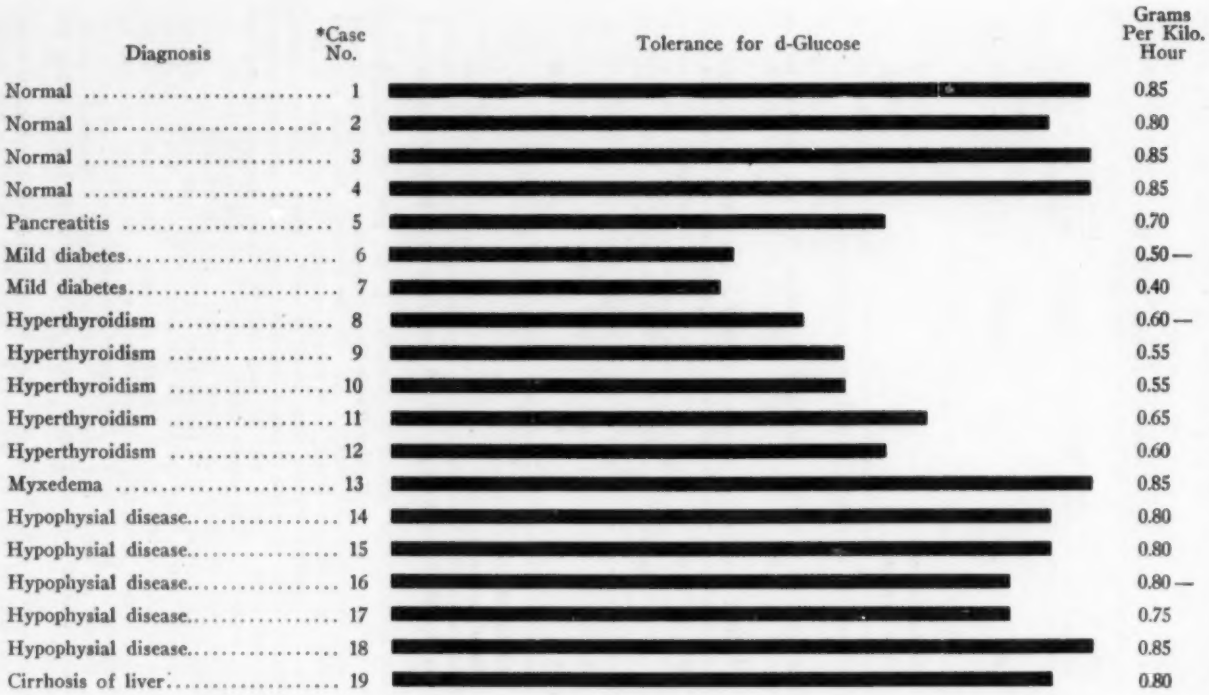
Tolerance lies between 0.8 and 0.9 gm. per kilogram per hour.

CASE 2.—P. G., a healthy woman, aged 21, weight 60 kg., rested in bed on the day of the test.

TABLE 2.—GLUCOSE SOLUTION, 18 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	4.45	28	Trace*	0.16	0.77
0.9	5	20	+	0.23	1.45
Subsequent loss					?
Total glycosuria					2.22+

* During the last three minutes of injection at the 0.8 gm. rate the pump accidentally accelerated. This accounts for the trace of sugar found in the urine. The tolerance, therefore, probably lies above 0.8 but below 0.9 gm. per kilogram per hour.



*Numbers refer to case histories.

CASE 3.—W. S., a healthy man, aged 35, weight 73.2 kg., rested on the day of the test.

TABLE 3.—GLUCOSE SOLUTION, 40.91 PER CENT.

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.85	2.38	32	Trace	0.23	0.15
0.9	2.66	30	+	0.86	1.12
Subsequent loss					0.76
Total glycosuria					2.03

Tolerance lies very close to 0.85 gm. per kilogram per hour.

CASE 4.—J. V., a healthy man, aged 25, weight 75.45 kg., rested in bed on the day of the test.

TABLE 4.—GLUCOSE SOLUTION, 19.75 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	5.1	30	0		
0.9	5.73	30	+	0.64	1.86
Subsequent loss					1.02
Total glycosuria					2.88

Tolerance lies between 0.8 and 0.9 gm. per kilogram of body weight per hour.

CASE 5.—Diagnosis, chronic pancreatitis. J. W., aged 45, was admitted to the service of Dr. J. B. Herrick at the Presbyterian Hospital on Nov. 6, 1915, with complaints of jaundice and intense itching. He gave a history of syphilis in 1888, for which he received treatment, herpes zoster in 1911, and in 1912 jaundice without pain, fever or chills, which lasted two weeks. In August, 1915, he again became jaundiced, this time with cold sweats, a chill and fever. There was no pain and the fever disappeared, but the jaundice continued. The patient lost in weight from 138 to 124 pounds.

Examination disclosed an intense icterus. The gallbladder was barely palpable, but not tender. The temperature was recorded as 100.6 on the day of admission, but remained normal for the next two weeks. The urine showed a large amount of bile, but no albumin or sugar. The stools were mushy, clay colored, gave a strongly positive Weber test for blood, and contained fat in abundance and some starch. The stomach contents after Ewald's test breakfasts showed no blood and were of normal acidities. Duodenal contents, aspirated by means of an Einhorn tube, contained blood and ferments, but no bile.

A diagnosis of organic disease of the head of the pancreas was made, which was confirmed by operation on Dec. 6, 1915. The patient showed marked

improvement following operation, gaining 12 pounds in weight. A second operation was made on Jan. 22, 1916, and the mass in the head of the pancreas was found to be smaller. Probable diagnosis was made of ulcer of the duodenum with secondary chronic pancreatitis and obstructive jaundice.

An intravenous glucose tolerance test on this patient made Nov. 22, 1915, gave the results shown in Table 5. The weight of patient was 54.3 kg.

TABLE 5.—GLUCOSE SOLUTION, 20.25 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.2	0.89	30	0		
0.5	2.24	70	0		
0.7	3.13	82	Trace	0.1	0.95
0.9	4.02	85	++	0.66	2.09

The threshold of tolerance lies at or very close to 0.7 gm. per kilogram of bodyweight per hour, which is slightly below normal.

CASE 6.—Diagnosis, mild diabetes. R. D., a physician, aged 33, showed a trace of sugar in the urine in a recent examination. In one twenty-four hour specimen this had amounted to 0.2 per cent. He had suffered from an attack of appendicitis and underwent an operation in 1911. Two sisters had died of tuberculosis and one brother was obese, weighing 225 pounds.

The patient was a tall, muscular man. The tonsils were small and cryptic. There were a few fillings in the teeth and the gums were retracted at the roots of the left upper molars. The thyroid was not enlarged. A urinalysis was negative.

An intravenous glucose tolerance test was made and resulted as shown in Table 6. The weight of the patient was 83.2 kg.

TABLE 6.—GLUCOSE SOLUTION, 21.94 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	3.16	30	++	0.69	0.53
				Subsequent loss	1.19+
				Total glycosuria	1.72+

The threshold of tolerance lies well below 0.5 gm. per kilogram of bodyweight per hour. The urine was only collected for one hour after the injection stopped.

CASE 7.—Diagnosis, mild diabetes. W. K., aged 49, was admitted to the service of Dr. Billings at the Presbyterian Hospital on June 23, 1916. His complaints were aching pains in the right thigh and the suspicion of diabetes.

He gave a history of excellent health up to 1910, when sugar was found in his urine. At that time he was losing weight, had excessive thirst and hunger and polyuria. He was placed on a restricted diet and was soon apparently normal. During the last year he has had rather frequent urination and for the

last three months has suffered from pains in the right thigh and a feeling of weakness in the legs on ascending stairs.

Examination showed a well-nourished man of average height. The teeth were badly discolored and decayed and the Roentgen ray revealed a chronic abscess at the root of one molar. The gums were retracted. A slight systolic murmur was audible at the apex. In all other respects the examination was negative.

Urinalysis of twenty-four-hour specimens showed 1,500 to 1,800 c.c., with specific gravities of 1.010 and 1.013. No reduction of Haines' solution was obtained and there was no evidence of diacetic acid or acetone.

An intravenous d-glucose tolerance test was made on June 26 with results as shown in Table 7. The weight of the patient was 75.4 kg.

TABLE 7.—Glucose Solution, 16.4 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.3	2.29	90	0		
0.5	3.06	80	+	0.5	2.225

The threshold of tolerance lies between 0.3 and 0.5 gm. per kilogram of body weight per hour.

Case 8.—Diagnosis, hyperthyroidism. M. R., a girl, aged 19, complained on admission of goiter, nervousness, dyspnea, palpitation, and edema of the feet. The trouble began as nervousness eighteen months ago. Six months later the thyroid enlarged and the eyes became prominent, and before admission the right lower jaw had often been swollen and painful. Menstruation had been normal.

On examination the patient presented a marked exophthalmos, a fairly large goiter of uniform, firm consistence over which a double murmur could be auscultated, a fine tremor of the tongue and fingers and a pulse ranging from 120 to 140. Adenoids and tonsils were hypertrophic. In the tonsils were deep crypts which contained pus. There were several broken-down teeth at the roots of which abscesses were demonstrable.

Blood counts revealed a moderate anemia and a mononucleosis of from 40 to 46 per cent. Urinary examinations showed an albuminuria of less than 0.1 per cent., a few casts, but no erythrocytes and no sugar.

An intravenous glucose tolerance test was made on this patient with results as shown in Table 8. The weight of the patient was 70 kg.

TABLE 8.—Glucose Solution, 21.8 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.6	3.21	60	+	0.267	1.92
Subsequent loss					2.12
Total glycosuria					4.04

The threshold of tolerance lies below 0.6 gm. per kilogram of body weight per hour.

CASE 9.—Diagnosis, hyperthyroidism. E. L., a woman, aged 32, was admitted to the service of Dr. B. W. Sippy at the Presbyterian Hospital on Jan. 16, 1916, with complaints of goiter, bulging eyes, palpitating heart, nervousness and weakness. The family history was remarkable in that all the female members of the mother's side, including the grandmother, had large goiters. None had suffered from symptoms of exophthalmic goiter.

The patient had no goiter until the onset of the present trouble, but was always nervous. She had measles at 9, and had suffered from catarrh of the nose and throat from her eighteenth year. At 25 came an acute attack of tonsillitis. Her present illness commenced two months before admission with painful swelling of the thyroid. The pain disappeared in a week, but the swelling persisted; exophthalmos, palpitation and tremors appeared; she grew very nervous and lost weight rapidly.

Examination revealed a young woman in a fair state of nutrition. Exophthalmos was extreme and von Graefe, Möbius and Stellwag signs were present. The goiter was of medium size and of a uniformly firm consistence. A systolic bruit was heard over it. Submanubrial dulness was 7 cm. wide (thymus?). The heart was normal in size, the pulse 112 and regular. The leukocyte count was 8,500 with 45 per cent. mononuclears. The urine was normal on repeated examination.

An intravenous sugar tolerance test was made with results as shown in Table 9. The weight of the patient was 62.3 kg.

TABLE 9.—GLUCOSE SOLUTION, 17.6 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	2.95	45	0		
0.6	3.54	46	+	0.5	3.23
Subsequent loss					3.41
Total glycosuria					6.64

Tolerance lies between 0.5 and 0.6 gm. per kilogram per hour.

CASE 10.—Diagnosis, hyperthyroidism. A. S., a man, aged 41, was admitted to the service of Dr. C. B. Davis of the Presbyterian Hospital on Aug. 16, 1915, with complaints of goiter, prominence of the eyes, palpitation, nervousness and loss of weight. His disease began in 1903 with thyroid swelling and nervousness. Exophthalmos occurred in 1904 and until 1905 he was very ill. Then followed a period of improvement, lasting until 1913, but after 1913 he suffered from extreme nervousness and palpitation and has lost twenty-five pounds in weight. Sugar has been found in the urine on several occasions.

When examined the patient presented the typical appearance of exophthalmic goiter. He was very thin, very weak and highly nervous. Exophthalmos was extreme, and von Graefe, Möbius and Stellwag signs were positive. The tumor of the neck was large and of a uniformly hard consistence. Over it was heard a systolic, diastolic bruit. The veins of the neck were distended. The heart was enlarged to the left, the apex lying in the fourth space, 11 cm. to the left of the midsternal line. A soft systolic murmur occurred over the apex; a louder systolic murmur was heard at the base and this was transmitted to the neck. The pulse rate was 104. A blood count on the day of admission gave 6,150 whites, with a mononuclear percentage of 29. The urine was normal.

An alimentary test for tolerance, 50 gm. of glucose, was made on Aug. 17, 1915, and 1.6 per cent. glycosuria obtained. Seventeen gm. of sugar were excreted and traces of sugar appeared in the urine for several days.

On Aug. 24, 1915, the upper poles of the thyroid were ligated.

The intravenous tolerance test was made on Feb. 3, 1916, with results as shown in Table 10. The weight of the patient was 53.2 kg.

TABLE 10.—Glucose Solution, 17.67 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	2.51	31	0		
0.6	3.01	33	++	0.48	1.73
Subsequent loss					13.39
Total glycosuria					15.12

Tolerance lies between 0.5 and 0.6 gm. per kilogram per hour.

Case 11.—Diagnosis, hyperthyroidism, myositis. J. S., aged 52, was admitted to the Presbyterian Hospital on the service of Dr. Frank Billings with complaints of soreness and weakness of the muscles. The trouble started acutely in May, 1915, with a fever of 104, headache, great muscle soreness and severe weakness. He lost 50 pounds in weight.

Examination revealed extensive muscular atrophies and contractures and tenderness of many tendons. There were no deformities of the joints. In addition, the thyroid was moderately enlarged and there was a fine tremor of the hands and tongue. Ocular symptoms were absent. There was also a diffuse dilatation of the heart and a loud mitral systolic murmur could be heard at the apex. Both great toe nails were ingrown and infected, the tonsils appeared diseased and the teeth were in bad condition. Blood counts gave 3,700,000 erythrocytes, 65 per cent. hemoglobin and 6,300 leukocytes, of which 42 per cent. were mononuclears. Uranalyses were normal. The pulse was fast, ranging from 90 to 120. The temperature proved irregular, occasionally mounting to 101 or 102 F.

TABLE 11.—Glucose Solution, 22.36 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	1.75	44	0		
0.6	2.1	41	0		
0.7	2.45	46	+	0.21	0.34
Subsequent loss					1.94
Total glycosuria					1.97

The threshold of tolerance lies below 0.7 gm. per kilogram of body weight per hour.

From October 6 to October 12 the patient received 9 gm. of thyroid extract daily and within forty-eight hours the thyroid became more prominent and the nervousness and tremors increased. The thyroid extract was discontinued. The tonsils were removed and the teeth attended to.

An oral sugar tolerance test was made on October 22. One hundred gm. of glucose given on the fasting stomach produced no glycosuria.

An intravenous glucose tolerance test was made on November 29, and resulted as shown in Table 11. The weight of the patient was 47 kg.

CASE 12.—Diagnosis, hyperthyroidism. A. W., a woman, aged 30, suffered from goiter, dyspnea, and palpitation for four years. An attack of tonsillitis with fever immediately preceded the first appearance of these symptoms. Another severe attack of tonsillitis three years later was followed at once by nervousness, tachycardia and loss of weight.

The patient presented a moderate enlargement of the isthmus of the thyroid and a von Graefe. The pulse ranged from 90 to 110. Exophthalmos and tremor were absent. The tonsils were atrophic, but showed in their scarred fibrous surfaces and adhesion to the pillars definite evidence of infection. A moderate anemia was found. The leukocyte count was 8,000 and the mononucleosis 45 per cent. The urine was normal.

An intravenous tolerance test resulted as shown in Table 13. The weight of the patient was 49.54 kg.

TABLE 12.—GLUCOSE SOLUTION, 40.59 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	1.02	60	0		
0.7	1.42	30	++	0.43	0.75
Subsequent loss					0.95
Total glycosuria					1.70

The threshold of tolerance lies well below 0.7 gm., but above 0.5 gm. per kilogram of body weight per hour.

CASE 13.—Diagnosis, myxedema. Mrs. A. L., aged 64, was admitted to the Presbyterian Hospital on Aug. 15, 1916, with complaints of thickened skin, stiffness of the hands and feet and mental dulness. The family history was negative except for one daughter, who developed an exophthalmic goiter when 40 years of age. The patient has had twelve healthy children, and gives no history of syphilis. She was always well up to her 61st year, when symptoms of the present trouble appeared.

The diagnosis of myxedema was made at the Central Free Dispensary in 1913, and for several months the patient received thyroid extract, but for the last two years she has been away and has had no treatment.

Examination showed the patient to be an elderly Jewish woman who appeared uninterested in her surroundings and mentally dull. The skin was dry and stretched tight over the arms and legs. It had a board-like or bacony feel, especially over the face and arms. There were no axillary hairs, the eyebrows were scanty, and the hair of the scalp was thin and very dry. The pulse was slow, 60 to 70, and the respiration was shallow. The thyroid was not palpable. The lungs had normal resonance, and the breath sounds were clear, except for occasional moist râles at the base. The abdomen was negative.

The temperature was normal. The blood count gave 3,780,000 red cells, 8,100 white and a hemoglobin percentage of 75. The urine was normal in amount and free from albumin or sugar.

The intravenous tolerance test gave results as shown in Table 12. The weight of the patient was 70 kg.

TABLE 13.—Glucose Solution, 18.21 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	5.12	42	0		
1	6.41	25	++	0.97	2.14

Subsequent loss not determined.

The second injection rate is well above the patient's tolerance, which undoubtedly lies between 0.8 and 0.9, the normal limits.

Case 14.—Diagnosis, acromegaly. W. F., aged 40, was admitted to the service of Dr. Dean Lewis of the Presbyterian Hospital in 1913, with complaints of blindness and an increase in the growth of the hands, feet and head. His attention was first attracted to his condition in 1905, when he found that his hats were small. A year later his feet outgrew his shoes. In 1907 he was troubled with blurred vision and photophobia. His color sense was lost and finally in 1909 he became totally blind. His weight remained nearly stationary, about 225 pounds, during the entire course of the disease.

Examination revealed conditions typical of acromegaly, hypertrophied bones of the calvarium and jaw, huge hands and enormous feet. The skin was thick and the hair course and dry. An examination of the eyes revealed a complete amblyopia, due to a bilateral optic atrophy. There was also a marked horizontal nystagmus to the left. A Roentgen-ray plate of the skull showed an enormous sella.

The patient remained in the hospital until May, 1915. During this interval the temperature was practically normal and the pulse varied between 80 and 100. Twenty-four-hour urinary volumes were rather high, at times over 3,000 c.c. The urine often contained small amounts of albumin and a few casts, but never any sugar.

TABLE 14.—Glucose Solution, 19.43 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	6.91	35	Trace	0.16	0.03
1	8.64	30	++	0.8	0.29
Subsequent loss					2.01
Total glycosuria					2.33

The threshold of tolerance lies very close to 0.8 gm. per kilogram of body weight per hour.

An oral glucose tolerance test was made on March 15, 1915. On giving 125 c.c. of glucose at 7 a. m., no glycosuria resulted.

The patient returned to the hospital in November. His condition had remained practically stationary. An intravenous tolerance test was made and resulted as shown in Table 14. The weight of the patient was 103.6 kg.

CASE 15.—Diagnosis, acromegaly. C. H., man aged 38 was admitted to the service of Dr. Dean Lewis of the Presbyterian Hospital on Jan. 4, 1916, with complaints of diminishing vision, increasing size, headache, weakness and loss of sexual desire. The patient was an adopted child and could tell nothing about his parents. At 7 years of age he had a severe illness the nature of which he ignores, and in 1906 suffered from a light attack of malaria. He was married in 1915 and had no children. The present illness seems to have begun in 1913, when he began to increase in size and weight. He is now 6 feet 1 inch tall and weighs 210 pounds. His former weight was 185. His feet and hands are bigger and he is obliged to buy 7¼ inch size of hats instead of his former size 6⅞. Visual disturbance first occurred in February, 1915.

On examination the findings were those typical of acromegaly and roentgenograms of the hypophysial region revealed a sella very much enlarged. The leukocyte count was 7,600, with 58 per cent. mononuclears. The urine was normal on repeated examination. Two hundred gm. of glucose were given by mouth without producing glycosuria.

An intravenous tolerance test resulted as shown in Table 15. The weight of the patient was 95.5 kg.

TABLE 15.—GLUCOSE SOLUTION, 19.01 PER CENT.

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.7	5.25	30	0		
0.9	7.5	30	++	3.18	2.7
Subsequent loss					7.98
Total glycosuria					10.68

Tolerance lies below 0.9 gm., but above 0.7 gm. per kilogram per hour.

CASE 16.—Diagnosis, hypophysial disease (Frölich syndrome). H. C., a girl, aged 14, complained of obesity, delayed sexual development and frontal headache. The headaches began when she was about 10 years old. At 12 obesity was noticeable. At 13 she became uncertain of her balance and would sometimes fall to the ground, without, however, losing consciousness. She has never menstruated.

Examination revealed a corpulent child of small stature, mentally very bright. The head was larger than normal. The vision was good and the color fields were unaltered. The pupils, however, reacted sluggishly and both optic disks were abnormally pale, so that an early optic atrophy was diagnosed. Secondary sexual characteristics were lacking.

Urine examinations were completely negative and the twenty-four-hour urinary amounts were normal. The spinal fluid contained only 5 cells per c.mm. and gave negative Wassermann, Nonne and Lange tests. Roentgen-ray plates of the head showed a sella much increased in size. A subsequent decompression operation revealed marked intracranial pressure.

An intravenous glucose tolerance test was made on this patient before the decompression operation was performed and resulted as shown in Table 16. The weight of the patient was 47 kg.

TABLE 16.—GLUCOSE SOLUTION, 19.43 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.8	2.23	42	+	0.31	0.372
Subsequent loss					0.405
Total glycosuria					0.777

The threshold of tolerance lies a little below 0.8 gm. per kilogram of body weight per hour. There is certainly no increase over normal.

CASE 17.—Diagnosis, hypophysial disease (gigantism?). T. W., a man, aged 26, was admitted to the service of Dr. D. P. Abbott at the Presbyterian Hospital on Jan. 10, 1916, with complaints of temporal headaches, weakness and nervousness. The headaches were of only a few days' duration. The weakness was not great. The nervousness had been present since childhood. The patient had no severe illnesses other than a chronic infection of the right ear which began early in childhood and only healed in 1912. He was, however, slow in learning to walk (2 years), was always big for his age and had always been backward in school. His family history was negative and venereal infection was denied.

Examination revealed a man 6 feet 1 inch tall, and big in proportion. The sexual development, pubic hair, etc., appeared normal. There was an old perforation in the right ear drum. A roentgenogram of the hypophysial region showed an unusually small sella and it was thought probable that a correlation existed between this and the rather peculiar development.

An intravenous glucose tolerance test resulted as shown in Table 17. The weight of the patient was 80.7 kg.

TABLE 17.—GLUCOSE SOLUTION, 19.2 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.2	1.4	30	0		
0.7	4.9	30	0		
0.8	5.6	30	++	.....	Not determined

Tolerance lies between 0.7 and 0.8 gm. per kilogram per hour. It may be subnormal, but is certainly not increased.

Blood sugar determinations were made before and after the injections by Dr. G. Pearce and showed a percentage of 0.115 and 0.212, respectively.

CASE 18.—Diagnosis, hypophysial disease, diabetes insipidus. M. L., a man, aged 40, was admitted on the service of Dr. Joseph Miller at the Cook County Hospital in August, 1915. His complaints were polyuria and sexual impotence.

The first symptoms of disease occurred in 1907 and consisted of severe headache, occasional vomiting and excessive thirst. He would drink from 10 to 12 gallons of water a day. Sexual power was lost in 1911. Since 1913 he has been free from headaches and the thirst has been somewhat less. The appetite has always been moderate. He had four or five gonorrheal infections, and in 1901 a genital chancre. He was treated for this and no secondary symptoms of syphilis followed.

Examination revealed a moderately corpulent man of medium height and with small bones. The pubic hairs were found scanty and had a feminine distribution. The beard was very thin. Penis and testicles were small. In the right eye was a cataract, in the left the vision was good, but the red and green color fields showed some interlacing of their margins. The urine was found to be large in amount, the twenty-four-hour specimens containing from 3,000 to 6,000 c.c. The specific gravity was low and sugar was absent. Roentgenograms of the head revealed a slight enlargement of the sella and destruction of the posterior clinoid processes.

The intravenous glucose tolerance test resulted as shown in Table 18. The weight of the patient was 63.6 kg.

TABLE 18.—GLUCOSE SOLUTION, 20.11 PER CENT. BY POLARISCOPE

Rate of Injection		Minutes of Injection	Urine Glucose		
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope	Total Gm.
0.5	2.54	43	0		
0.6	3.16	80	0		
0.8	4.22	60	0		
0.9	4.75	87	+	0.29	0.80
Subsequent loss					0.86
Total glycosuria					1.45

The threshold of tolerance lies between 0.8 and 0.9 gm. per kilogram of body weight per hour.

CASE 19.—Diagnosis, cirrhosis of the liver. G. R., a man, aged 47, was admitted to the service of Dr. Billings at the Presbyterian Hospital on June 29, 1916. His complaints were loss of weight, weakness and pigmentation of the skin.

The history contained a record of scarlet fever at the age of 11 and malaria at 25, but excepting these illnesses, good health up to the spring of 1916.

Since April he has felt weak, has decreased in weight from 202 to 162 pounds, and has observed a pigmentation of the skin of the entire body. There has never been any icterus of the sclera and the color of the skin is more brown than yellow. In May he visited the dispensary, and from there was sent to the hospital. His family and venereal records are negative, but for years he has been drinking daily very considerable quantities of beer and whisky.

Examination revealed a poorly nourished man of average height. The pigmentation of the skin was unequally distributed, the nipples, pubic region and axillae were very dark; there were no spots in the mouth and the sclera were clear. There was a moderate pyorrhea and the teeth were discolored. The chest was normal in shape, the lungs slightly emphysematous, the heart borders somewhat wider than normal. A slight systolic blow was heard at the apex. The abdomen was somewhat pendulous, but contained no fluid. The spleen was palpable during inspiration, very firm, smooth and not tender.

The upper border of the liver was found at the fourth rib; the lower border extended 6 cm. below the costal arch in the mammary line. The edge was firm and regular and the surface was smooth

The blood pressure, systolic, was 140, diastolic 70. Wassermann tests were negative. A blood count gave 3,500,000 erythrocytes, 4,000 leukocytes and 70 per cent. hemoglobin.

The urine was examined repeatedly without finding sugar or bile pigments. The stools contained bile in normal amount.

On July 2, 50 gm. of glucose were given on the empty stomach without leading to melituria. Levulose and galactose tolerance tests were omitted, owing to the impossibility of obtaining these sugars.

An intravenous d-glucose tolerance estimation, made on July 5, 1916, resulted as shown in Table 19. The weight of the patient was 74 kg.

TABLE 19.—Glucose Solution, 17.48 Per Cent. by Polariscope

Rate of Injection		Minutes of Injection	Urine Glucose	
Gm. per Kg. per Hr.	C.c. Solution per Min.		Haines' Test	Per Cent. by Polariscope
0.4	2.82	40	0	
0.6	4.23	20	0	
0.8	5.64	15	0	0

Tolerance is above 0.8 gm. per kilogram of body weight per hour and is apparently normal.